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For the Study of the

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American Heart Journal

VOL. 35 JUNE, 1948 No. 6

Original Communications

THE EFFECT OF ERGOT DERIVATIVES ON THE CIRCULATION IN MAN WITH SPECIAL REFERENCE TO TWO NEW HYDROGENATED COMPOUNDS (DIHYDROERGOTAMINE AND DIHYDROERGOCORNINE)

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CAPE TOWN, SOUTH AFRICA

ALTHOUGH Dale,[7] as early as 1906, clearly recognized two active principles in the ergot alkaloids, namely, the direct pharmacologic effect on smooth muscle and the inhibition of sympathetic activity, it was mainly for the former that ergot preparations found widespread therapeutic application, particularly in obstetrical practice. The principle responsibile for the inhibition of sympathetic activity, however, remained more of pharmacologic and physiologic interest except, perhaps, in the treatment of migraine where this component may play its part.[1] Recent developments in sympathetic surgery, particularly with regard to essential hypertension, which implicate the sympathetic nervous system, if not in the genesis then at least in the maintenance of the raised blood pressure, have focused attention anew on sympathicolytic drugs.[14] By adding a purely sympathicolytic drug to the physician's armamentarium, it may be possible to offer some hope of relief to the vast number of cases of neurovascular disorders, and perhaps replace splanchnicectomy by medicinal measures in certain cases of hypertension. It is the purpose of this paper to investigate two new (hydrogenated) derivatives of ergot (dihydroergotamine and dihydroergocornine) as to their action on the cardiovascular system with particular reference to their sympathicolytic properties, and to compare their action with that observed following the administration of ergotamine tartrate (Gynergen).

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*Fellow of the Swiss Foundation for Fellowships in the field of Medicine and Biology.

THE DRUGS

Dale's original experiments were carried out with crude ergot extracts and ergotoxine. The latter was isolated in 1906 by Barger and Carr,[2] and by Kraft.[23] There was no doubt that ergotoxine was not a pure substance and in 1918, Stoll[36] isolated ergotamine which, pharmacologically, was practically indistinguishable from ergotoxine[9] but one-half as toxic.[25] Ergotamine quickly found widespread therapeutic application because of its prompt and powerful effect on the uterine muscle. Its beneficial effect in migraine was first recognized by Maier[26] and has since become one of the main indications in the usage for this drug. In 1935, a new ergot alkaloid was independently isolated by Stoll and Burckhardt,[38] Dudley and Moir,[10] Thompson,[44] and Kharasch and Legault,[21] which the various workers termed ergobasine, ergometrine, ergostetrine, and ergotocine, respectively. In 1936, a joint report by the teams concerned[22] established the chemical identity of the respective principles. The new drug had a marked and almost selective oxytocic action on uterine muscle. During the same period, Smith and Timmis[34] (1932) and Jacobs and Craig (1935)[19] succeeded in identifying lysergic acid as the principal and characteristic constituent of all ergot alkaloids, and in 1938 its formula was definitely established by Jacobs and Craig.[20] In the same year, Stoll and Hofmann[39] achieved the synthesis of ergobasine.

Three additional alkaloids were isolated from ergotoxine by the same authors[40] in 1943, one of which had, however, already been known as ergocristine. The other two they termed ergokryptine and ergocornine. These three alkaloids were different from each other in both their chemical and physical properties. By 1943, therefore, the following alkaloids of the ergot group were known: ergotamine, ergobasine, ergokryptine, ergocornine, and ergocristine. Lysergic acid being readily transformable into its isomer, isolysergic acid, it follows that each of the various ergot alkaloids has its isomer which, however, is pharmacologically inert. It is the levorotatory of the two compounds which is pharmacologically active. All active compounds except ergobasine, which is purely oxytocic, contained both active principles; that is the direct effect on smooth muscle and the sympathicolytic component.

The next important step came from Stoll and Hofmann[41] when in 1943 they demonstrated that well-defined compounds of the ergot alkaloids could be obtained by hydrogenating the readily reducible double bond of their lysergic acid. In this way they produced four new compounds: dihydroergotamine, dihydroergocristine, dihydroergocornine, and dihydroergokryptine. These hydrogenated derivatives were less toxic and less emetic than the original alkaloids and it was found that hydrogenation increased the sympathicolytic effect and diminished or abolished the direct action on smooth muscle.[30,31,37,6,33,35]

It is this aspect, in particular, which makes the new compounds of special interest and which stimulated this study for which the following substances were available: ergotamine tartrate (Gynergen), dihydroergotamine (DHE 45), and dihydroergocornine (DHO 180).*

*The preparations were made available through the courtesy of Prof. E. Rothlin, Sandoz Limited, Basle, Switzerland.

METHODS AND MATERIAL

Continuous records of the peripheral circulation were obtained by means of the Goetz optical digital plethysmograph described in detail elsewhere.[11-13] This sensitive method not only allows correct registration of the height of the volume pulse, but also calculation of the arterial inflow at any one moment by means of the so-called venous congestion test.[13] As is seen in various tracings, the respiration was continuously recorded simultaneously with the plethysmogram, and the skin temperature of one or more digits measured by means of a mirror galvanometer and thermocouples. The blood pressure was taken at regular intervals by clinical methods and the heart rate, of course, was available from the plethysmogram. Electrocardiographic tracings were taken at various intervals in many individuals. The drugs were given either by continuous intravenous infusion or by instantaneous intravenous injection, the mode of administration being indicated on every figure or chart. For intravenous infusion two drips were set up, connected via a two-way tap to the needle, and by merely turning the tap the drug could be administered or withheld without the patient being aware of it. Intravenous infusion was preferred because the interference resulting from the psychical trauma accompanying puncture of the vein could be avoided by administering saline for a considerable time before the drug was given. The drugs were tested on twenty-four subjects. In some of them, sympathectomies on one or more extremities had been carried out for various reasons, as stated in the legends of the respective figures. Additional information was available from twenty-four hypertensive patients who had been given the drugs for investigations reported elsewhere.[5] All patients used for this study reclined comfortably on a bed, usually wearing a suit of pajamas. The tests were carried out after a rest of thirty to sixty minutes. By that time, the volume records showed a minimum of spontaneous fluctuations in peripheral blood flow. If required, reflex vasodilatation was obtained by immersion of one or two extremities into a specially built tank containing water of 44 to 45° C., and covering the subject with blankets in order to prevent the dissipation of heat. An immersion heater connected in series with a thermostat and a stirring propeller were fixed in the tank to keep the water temperature constant at that level.

RESULTS

The Effect of Gynergen on the Circulation in Normally Innervated and Sympathectomized Limbs.—Intravenous injection of Gynergen produces inconstant and complex changes in the peripheral circulation, depending on the dose and because of the conflicting action of the two active constituents, that is, the direct constrictor effect on smooth muscle and the sympathicolytic (vasodilator) principle. The effect in the normally innervated limb is thus the result of the interaction of both these components, and therefore, both constriction or dilatation may be obtained depending entirely upon the dose and the preponderance of the action of one or the other component. This, in turn, depends on the state of the circulation (the vasomotor tone) in that particular subject at the time of

the injection. Obviously, if at the time of injection the vessels are dilated, sympathetic paralysis cannot be demonstrated. Vice versa, to demonstrate constriction the vessels should first be dilated. With vessels neither fully dilated nor fully constricted, Gynergen more often than not causes transient dilatation followed by prolonged constriction. However, occasionally the vessels, once

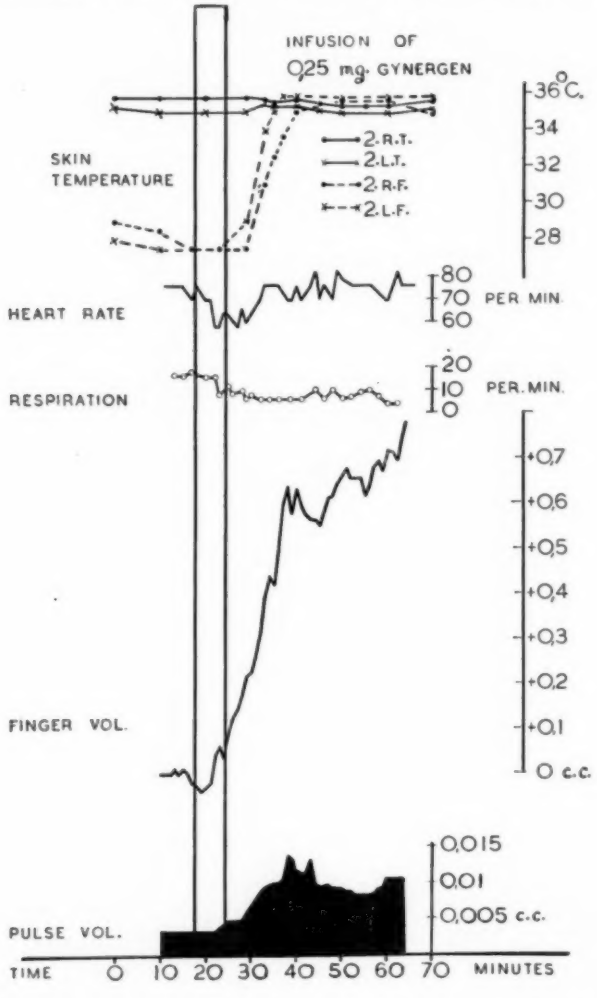

Fig. 1.—The effect of 0.25 mg. Gynergen (ergotamine tartrate) on the skin temperatures, heart rate, respiration, digital volume, and pulse volume (second left finger), all simultaneously recorded. The leg had been sympathectomized for ulcers in 1943. The upper extremities were normal. (Mrs. S. W.)

initiated into dilating, remain dilated thereafter, particularly after small doses (Fig. 1). In Fig. 1 a small dose (0.25 mg.) of Gynergen was given by intravenous drip over a period of ten minutes, and the skin temperature of four digits, heart rate, respiration, finger volume, and pulse volume were continuously recorded for the next hour. Before the administration, the vessels of the upper extremi-

ties were under a high vasomotor tone. Following the infusion, there was a definite and lasting increase in digital blood flow, as indicated by a rise in pulse volume from 0.003 c.c. to about 0.01 c.c. and a rise in finger volume by about 0.7 c.c. within twenty minutes. The skin temperatures of the fingers rose simultaneously from 28° to 35° C., while those of the sympathectomized and consequently dilated toes actually showed a slight drop. These findings are readily explained as resulting from the sympathicolytic effect of the drug. Fig. 2,*A* is an example of a case in which dilatation was less marked and followed by

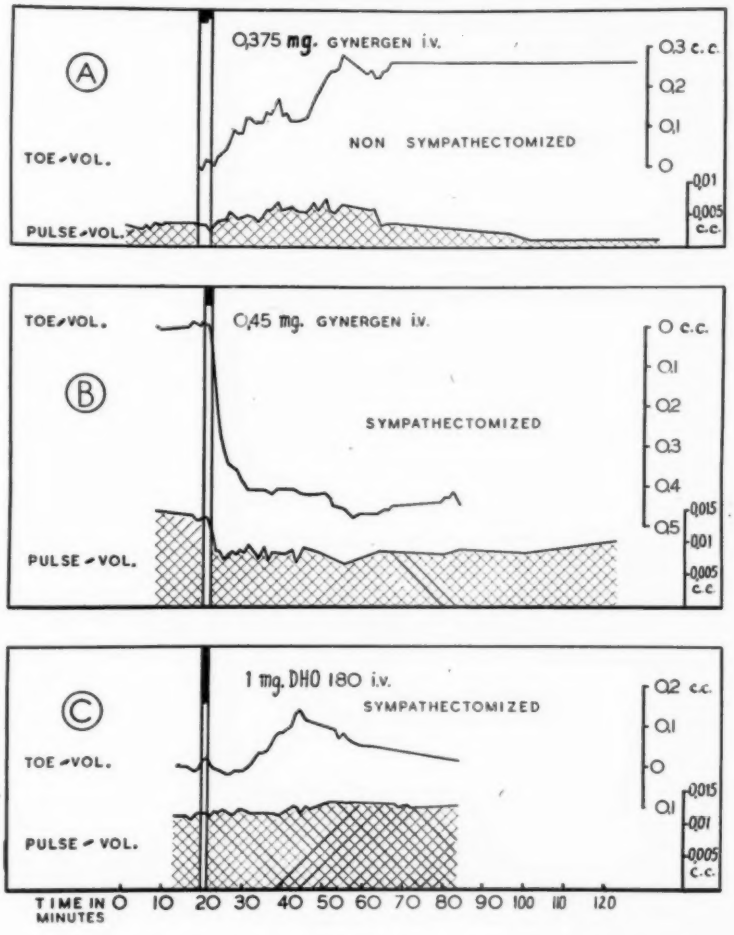

Fig. 2.—The effect of Gynergen on the peripheral blood flow (first right toe) before and fifteen days after lumbar sympathectomy for chronic crural ulcer as compared with the effect of DHO 180 on the sympathectomized limb of the same patient. For explanation, see text.

lasting constriction. The injection resulted in only a slight rise in pulse volume and thereafter full constriction of the peripheral vessels was recorded, the pulse volume becoming practically unregistrable after eighty minutes. The digital volume, too, showed only a slight increase (0.25 c.c.) within the first half hour,

and the skin temperatures did not change significantly. It is our experience that the sympathicolytic effect of the drug, that is, peripheral vasodilatation, is more readily recorded with the smaller doses (± 0.25 mg.) but that in larger doses peripheral constriction becomes more prominent, completely overshadowing any possible vasodilator effects of the sympathicolytic principle.

A detailed account of the changes in the pulse volume charted in Fig. 1 demonstrates that the vessels were almost fully constricted before injection and the pulse volume consequently registered only 0.0025 cubic centimeter. Ten minutes after the commencement of the intravenous drip, no changes in pulse volume were as yet recorded, although the respiration which before was regular (18 per minute) had already become markedly slowed and irregular. Fifteen minutes later a definite dilatation was recorded, the pulse volume having increased to 0.008 cubic centimeter. After a further twenty minutes the pulse volume was still the same and the respiration still depressed and irregular.

If the same dose of Gynergen (0.25 mg.) is given to the same patient but the circulation in the sympathectomized limbs* recorded, the same effect is always registered: definite vasoconstriction.

Fig. 2,*A* and *B*, is of particular interest since it illustrates the vascular reaction to Gynergen in one and the same digit before and after sympathectomy. Note the marked, immediate fall in pulse volume from 0.012 c.c. to 0.006 c.c. in the sympathectomized limb and the reduction in digital volume by 0.45 c.c., as against the transient dilatation before operation. Both digital volume and pulse volume remained at this low level in the sympathectomized limb for the following two hours during which the circulation was recorded.

The cuttings from the original film (Fig. 3) give a very clear picture of the powerful constriction obtained. Two minutes after the injection the pulse volume had already decreased from 0.012 c.c. to 0.008 c.c. and after five minutes it registered 0.006 c.c. only. Accompanying the reduction in pulse volume there was a steep fall in digital volume. The respiration was not markedly affected in this patient, although the dose was larger than in the patient concerned in Fig. 1. It should also be noted that, contrary to the reaction in the normal subject, puncture of the vein did not produce any vasomotor reaction of either pulse volume or digital volume, giving proof of the completeness of the denervation.

The effect of Gynergen in the sympathectomized limbs is obviously due to the pharmacologic action of the drug on the vessel wall, resulting in vasoconstriction. In none of our subjects did we record vasodilatation in a sympathectomized limb at any time and with any dose, indicating clearly that for its production the integrity of the sympathetic pathways is essential.

By testing the circulatory effect of the drug in both a normal and a sympathectomized extremity, the two components, that is, the direct pharmacologic

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*In all patients used for this study the sympathectomized limbs had been tested by various methods and the complete sympathetic denervation substantiated.

action and the sympathicolytic effect, can be separated and the direct acting principle can be demonstrated in its pure form. This procedure was followed for evaluating the effects of both dihydroergotamine and dihydroergocornine in the cases to be reported.

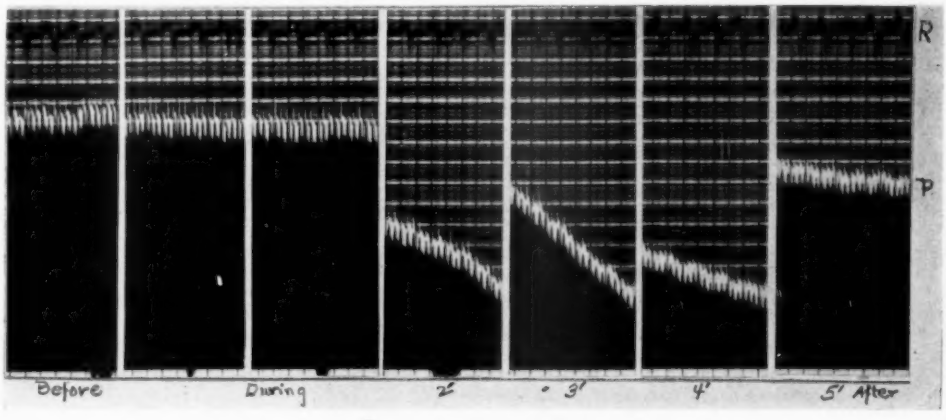

Fig. 3.—The effect of 0.45 mg. Gynergen on the respiration (R) and the plethysmogram (P) of a sympathectomized limb (first right toe), same test as Fig. 2, *B*. Note the drop in digital volume and pulse volume. The former has been adjusted several times between the cuttings.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Effect on Blood Pressure and Heart Rate: Without going into any detail, we should like to record that Gynergen invariably and in all doses caused a rise in systolic and diastolic blood pressure which varied between 10 and 40 per cent, with an average of 20 per cent, while the pulse rate tended to decrease by 10 to 15 per cent.

The Effect of Dihydroergotamine (DHE 45) on the Peripheral Circulation.—The effect of dihydroergotamine (DHE 45) on the peripheral circulation is essentially the same as that of ergotamine tartrate. Although Stoll[37] claims that dehydrogenation abolishes the direct action of the ergot alkaloids on smooth muscle, dihydroergotamine, like its original compound, ergotamine, in our experiments still caused marked constriction in the sympathectomized extremity. In Fig. 4 we reproduce the effect of an intravenous injection of 0.3 mg. dihydroergotamine on skin temperature, blood pressure, heart rate, digital volume, pulse volume, and rate of blood flow (as calculated by the venous congestion test, Goetz[13]), all simultaneously recorded in a patient in whom all four limbs had been sympathectomized. The chart is self-explanatory. There was an instantaneous diminution in peripheral blood flow as expressed by a drop in digital volume and pulse volume. The rate of blood flow actually diminished by about 60 per cent, while the blood pressure simultaneously rose from 115/80 to 140/90 and the heart rate dropped from 85 to 60 beats per minute. A detailed account of the effect of dihydroergotamine on the pulse volume, heart rate, and respiration is

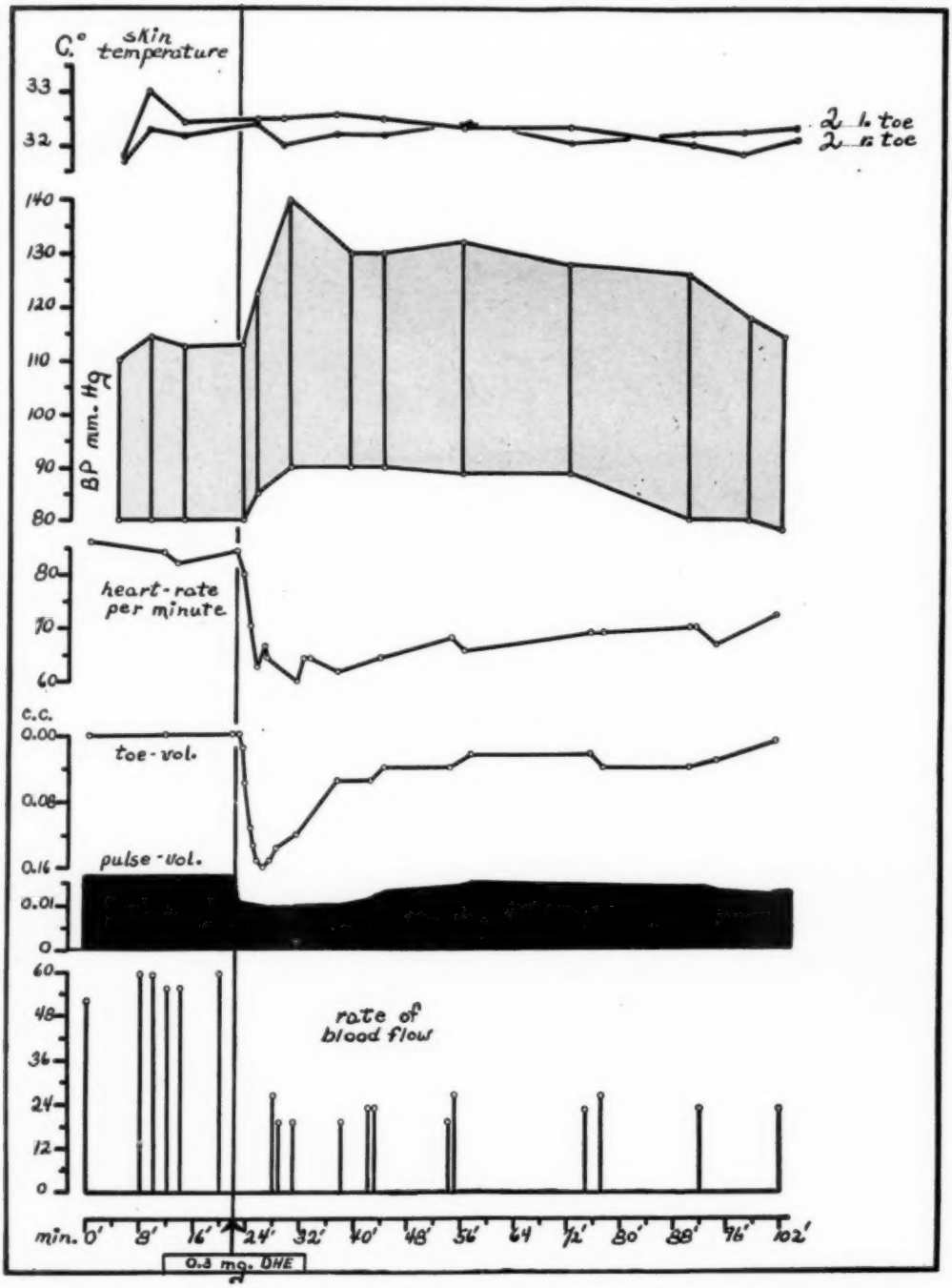

Fig. 4.—The effect of intravenous injection of 0.3 mg. dihydroergotamine (DHE 45) on the skin temperatures, blood pressure, heart rate, digital volume (first right toe), pulse volume, and rate of blood flow, all simultaneously recorded in a patient in whom all four limbs had been sympathectomized for Raynaud's disease. (Left upper, Jan. 21, 1944; right upper, Feb. 17, 1944; double lumbar sympathectomy, March 9, 1944.) For explanation see text.

available from Fig. 5. Before the injection, the pulse volume reached 0.018 cubic centimeter. Ten minutes after the injection, however, it was only 0.01 c.c., and the heart rate had dropped from 85 to 60 per minute during the same period. The changes occurring in the rate of blood flow, as calculated from venous congestion tests, are illustrated in Fig. 6. Before the injection the rise

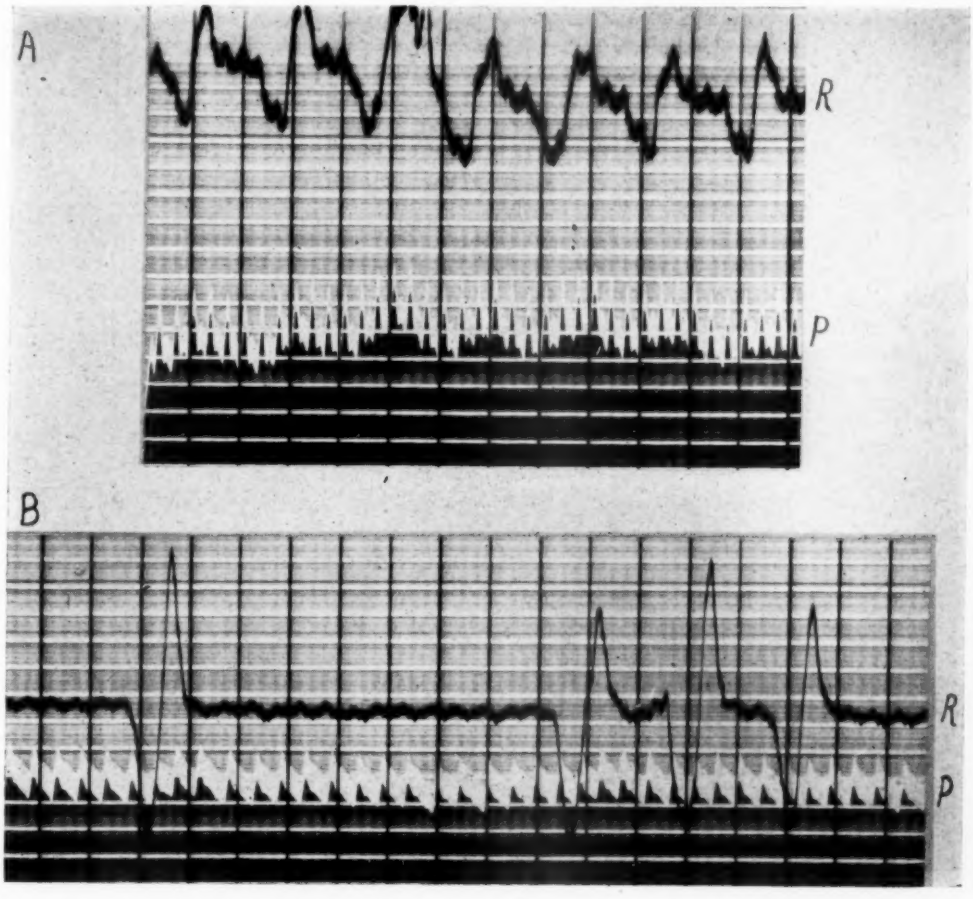

Fig. 5.—Cuttings of the plethysmographic records of the test charted in Fig. 4, showing respiration and pulse volume (first right toe) of sympathectomized limb before, and following, the injection of 0.3 mg. dihydroergotamine (DHE 45). Note slowing of pulse, vasoconstriction, and irregularities in respiration after DHE.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Reduction of original tracings to 2/3.

in digital volume on venous congestion amounted to about 0.07 c.c. during two seconds (Fig. 6,*A*). Ten minutes after the injection (Fig. 6,*B*) it had dropped to slightly more than 0.02 cubic centimeter. When calculating the rate of blood flow according to the formula previously given,[13] this fall corresponds to a

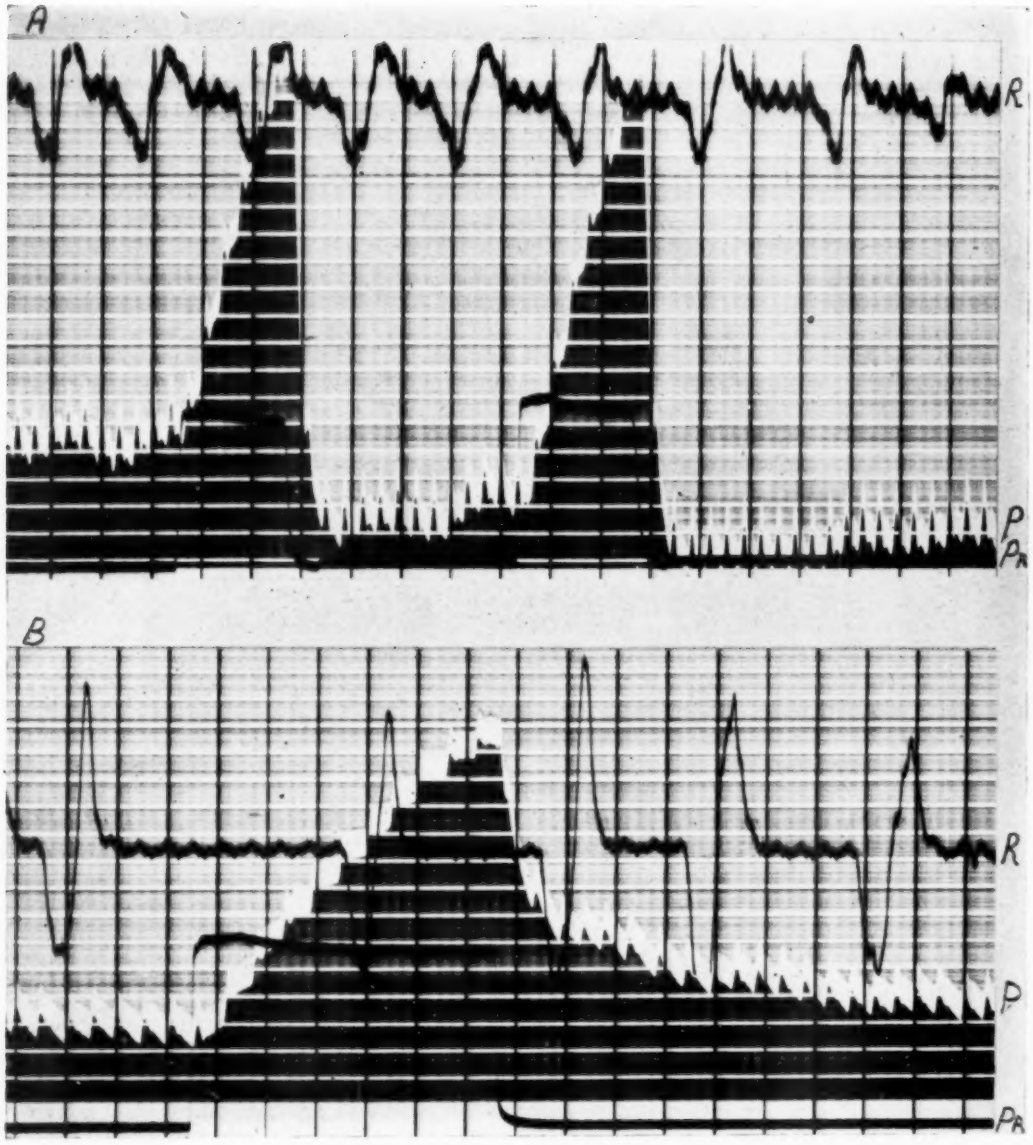

Fig. 6.—Venous congestion tests before and after 0.3 mg. dihydroergotamine in the same patient from whom Figs. 4 and 5 were obtained. *A*, Venous congestion before DHE. *B*, Five minutes after the injection of 0.3 mg. DHE. Note the reduction in arterial inflow, the diminution in the height of the pulse volume, and the irregularities in respiration.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Abbreviations: *R* = Respiration, *P* = plethysmogram, and *PR* = pressure for venous congestion test.

Reduction of original tracings to 2/3.

drop from 60 c.c. per minute for 100 c.c. of tissue to about 20 c.c. per minute for 100 c.c. of tissue. The changes in respiration are well illustrated in both Figs. 5 and 6.

This diminution in peripheral blood flow is not very transient. It takes at least eighty minutes for the blood pressure to return to normal, while the rate of blood flow and heart rate are not back to the original level even after that period. The effect of dihydroergotamine on the peripheral circulation has been the same in the sympathectomized limbs of all subjects, irrespective of the dose, and in Fig. 7 the reaction of the pulse volume and digital volume to the intravenous injection of 1.0 mg. dihydroergotamine in another patient leaves no doubt as to the constrictor effect of this drug on the peripheral vessels. The pulse volume decreased rapidly from 0.012 c.c to 0.005 c.c. as the drug was being

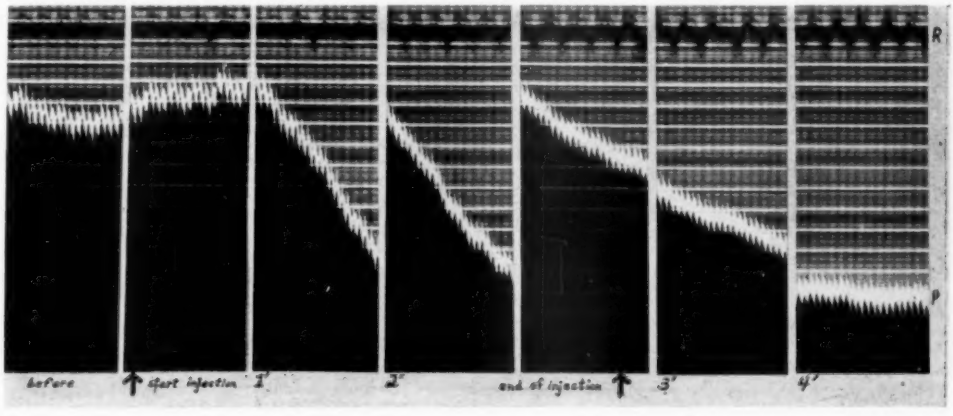

Fig. 7.—The effect of DHE (1.0 mg. intravenously) on the respiration and plethysmogram (first left toe) in a sympathectomized limb (double lumbar sympathectomy on Oct. 31, 1944, for crural ulcers). The digital volume has been adjusted several times between the cuttings following the injection of the drug.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

injected, and remained at the latter value thereafter. The toe volume, in consequence, decreased sharply. In Fig. 7, both pulse volume and digital volume reached their lowest values after about four minutes. The respiration of this subject was not markedly affected by the injection. In general, larger doses of dihydroergotamine are tolerated, since the drug is definitely less toxic than its original compound, ergotamine tartrate, as has already been stated by Rothlin[30] and Stoll.[37]

Consequently, the effect of dihydroergotamine (DHE 45) on the peripheral circulation in normally innervated limbs is, like that of ergotamine, a mixture of both the direct pharmacologic effect on the peripheral blood vessels and of the paralysis of sympathetic impulses. Therefore, like ergotamine, various reactions are obtained, depending upon the vasomotor tone and upon the dose. However, it appears that the direct pharmacologic action is less marked in this derivative than in the original compound.

As for the effect of dihydroergotamine on the blood pressure in normal subjects, the most common finding in our series was a rise in both the systolic and diastolic blood pressures. However, a definite fall, particularly following a transient rise, has been observed in a number of cases.

The Effect of Dihydroergocornine (DHO 180) on the Peripheral Circulation.—Contrary to the effect of both ergotamine and dihydroergotamine, the response of the peripheral circulation to dihydroergocornine, if present, is always the same, that is, vasodilatation. Fig. 8 illustrates the changes in pulse volume, digital volume, heart rate, and respiration observed after intravenous injection

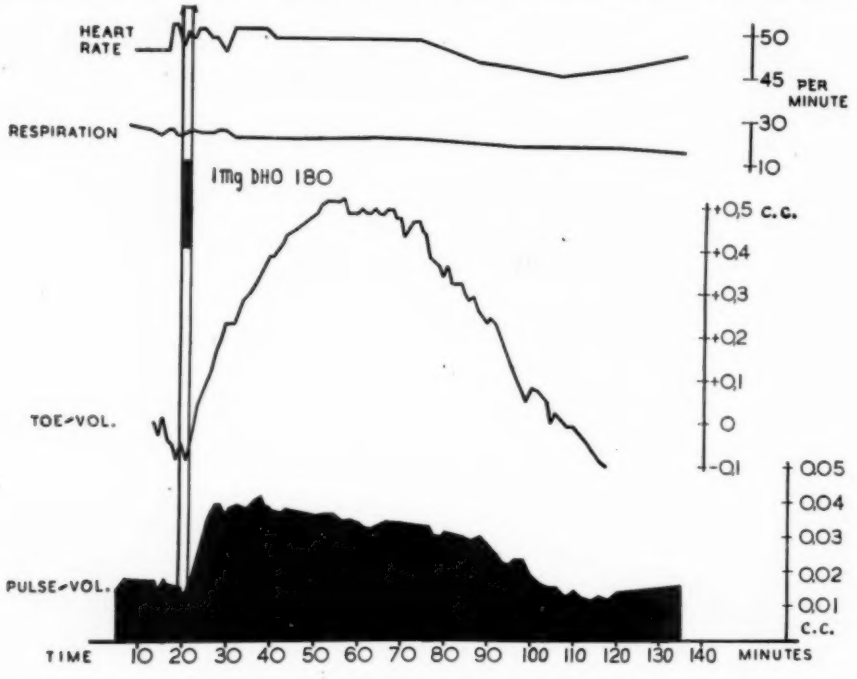

Fig. 8.—The effect of intravenous injection of 1.0 mg. dihydroergocornine (DHO 180) on the peripheral blood flow (first right toe), respiration, and heart rate in a normal subject. For explanation see text.

of 1.0 mg. dihydroergocornine (DHO 180) in a normal individual. Following the injection a marked dilatation was observed, being at its maximum about seven minutes following the injection. The pulse volume rose within a few minutes from 0.012 c.c. to 0.04 c.c., which means that the vascular tone had been completely abolished, and returned to the original height only after about two hours. The toe volume correspondingly increased by 0.5 cubic centimeter. In other subjects, the injection of dihydroergocornine resulted in an increase in the circulation to full vasodilatation level and the vessels remained fully dilated while under observation.

The changes in blood flow following the injection of 1.0 mg. dihydroergocornine are most striking in the cuttings from the original tracing (Fig. 9).

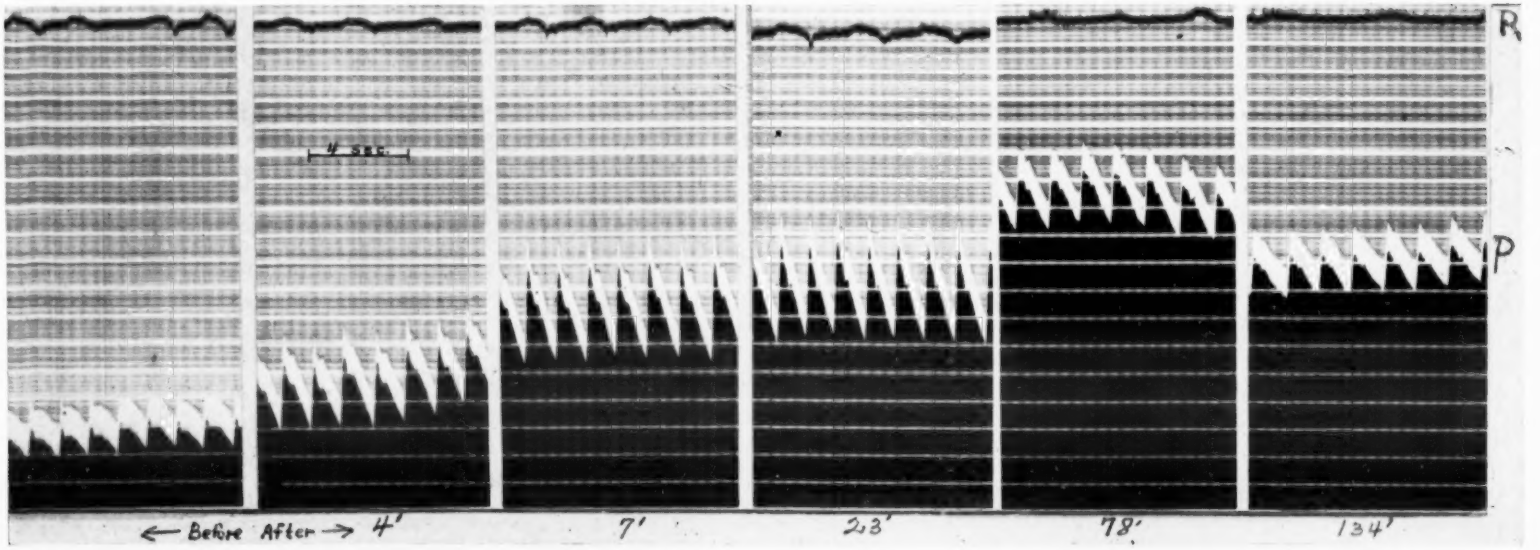

Fig. 9.—Cuttings from the plethysmographic record (first right toe), of the test charted in Fig. 8 (1.0 mg. DHO intravenously). The digital volume has been adjusted several times between the various cuttings.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Reduction of original tracings to 2/3.

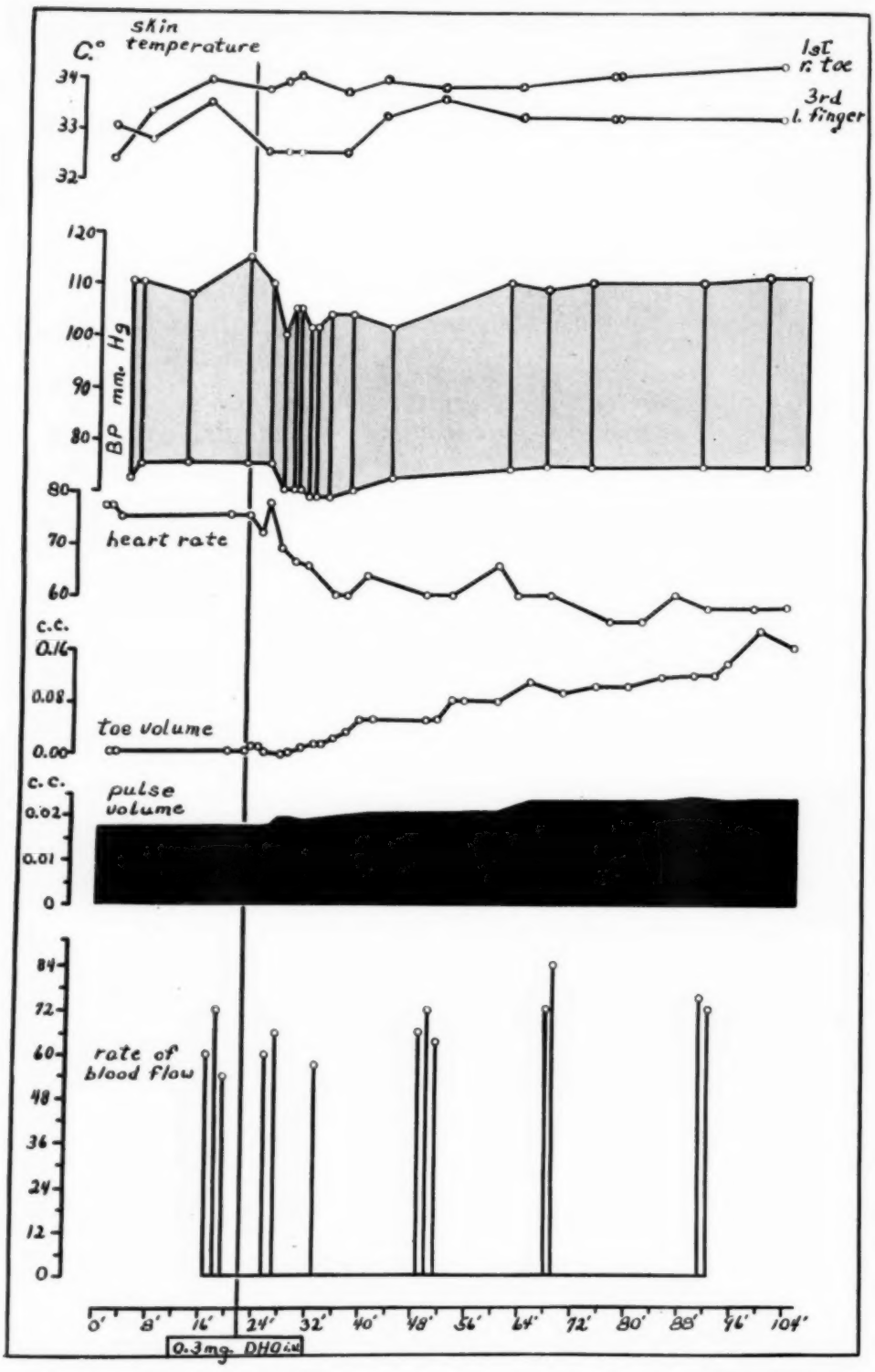

Fig. 10.—The effect of intravenous injection of 0.3 mg. dihydroergocornine (DHO 180) on the skin temperature, the blood pressure, heart rate, toe volume (first right toe), pulse volume, and rate of blood flow, all simultaneously recorded in a patient in whom all four limbs had been sympathectomized for Raynaud's disease (left upper limb, Jan. 21, 1944; right upper limb, Feb. 17, 1944; double lumbar sympathectomy, March 9, 1944). Compare with the effect of DHE in the same subject (Fig. 4). For explanation see text.

Before the injection the pulse volume registered 0.012 cubic centimeter. Four minutes after the injection it had risen to 0.025 c.c. and three minutes later its value was 0.035 c.c., remaining at that level for the next sixteen minutes. Seventy-eight minutes after the injection, the pulse volume was still increased, being 0.02 c.c., and only after two and one-half hours following the injection was the initial level of 0.012 c.c. reached.

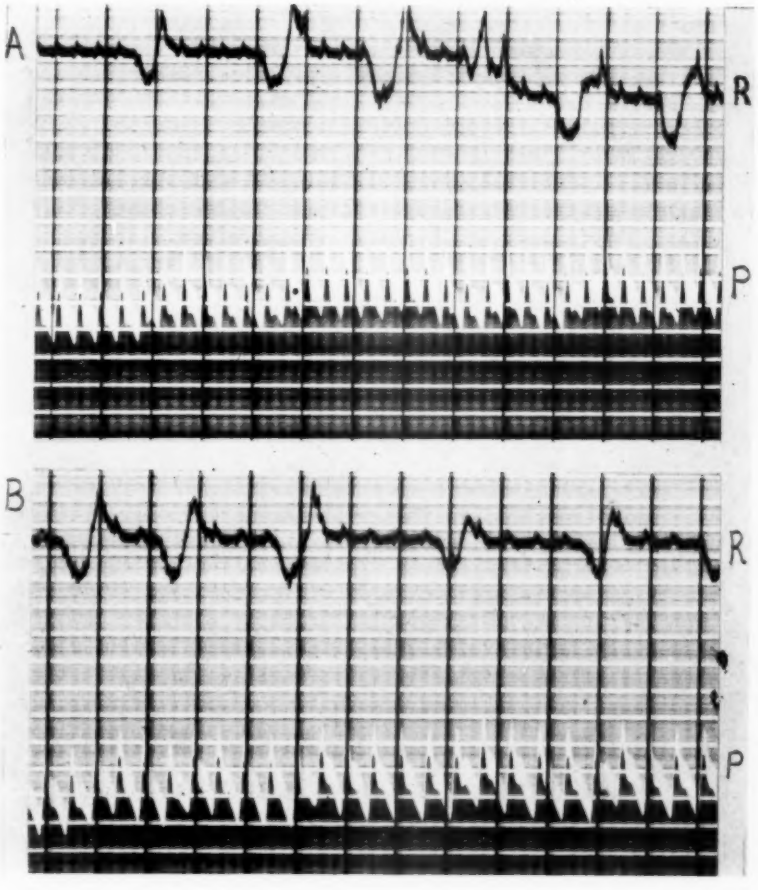

Fig. 11.—Cuttings from the original plethysmographic tracing to indicate the increase in pulse volume obtained following 0.3 mg. DHO and charted in Fig. 10. Note also the reduction in heart rate.
White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.
Ordinates = 2 seconds.
Reduction of original tracings to 2/3.

In the sympathectomized extremity, dihydroergocornine, in contrast to ergotamine and its hydrogenated compound, dihydroergotamine, did not produce any diminution in the peripheral blood flow in any of the twenty-four subjects examined. A typical example of its effect is illustrated in Fig. 10. The intravenous injection of 0.3 mg. dihydroergocornine produced a fall in blood

pressure and heart rate, while both pulse volume and digital volume actually increased slightly. Correspondingly, the rate of blood flow, as calculated from venous congestion tests, tended to be slightly greater. The increase in pulse volume, in our opinion, was not due to active vasodilatation but can be explained by an increase in the stroke volume of the heart associated with the fall in heart rate. The actual changes in pulse volume are very well illustrated in Fig. 11.

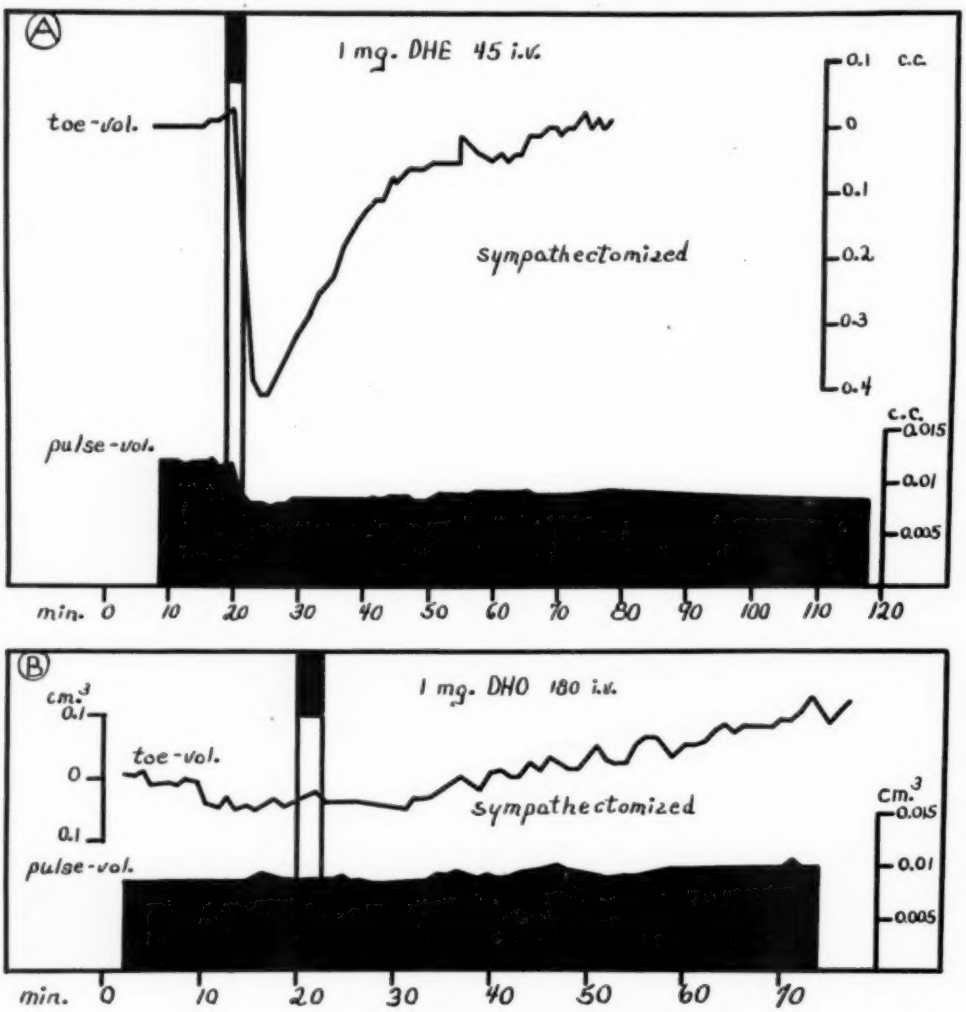

Fig. 12.— Comparison of the effect of 1.0 mg. DHE and 1.0 mg. DHO on the peripheral blood flow in a sympathectomized limb (double lumbar sympathectomy, Oct. 31, 1944, for crural ulcers). Note the marked reduction in blood flow following the injection of DHE and the absence of this constriction following the injection of DHO.

The difference in the action of the two drugs, that is, of dihydroergotamine and of dihydroergocornine, becomes very obvious when we compare the results obtained from the injection in one and the same subject (Fig. 12). The diminu-

tion, both in pulse volume and digital volume following dihydroergotamine, appears to be very pronounced when contrasted with the inertia of both following the injection of dihydroergocornine. The effects of dihydroergotamine and dihydroergocornine may also be compared by consulting Figs. 10 and 4, which were obtained in one and the same subject.

Two points emerge from these findings: first, that dihydroergocornine does not contain the principle acting directly on smooth muscle and causing peripheral vasoconstriction, but is purely vasodilator, and second, that this vasodilatation is not a direct effect on the smooth muscle but is dependent on the integrity of the sympathectic pathways. From experiments carried out by previous authors, we have to assume that we are dealing with the sympathicolytic component. Dihydroergocornine, therefore, acts purely as a sympathetic inhibitor.

Investigations concerning the effect of dihydroergocornine on the blood pressure have been reported elsewhere.[5] The effect depends entirely upon the dose. Small doses (up to 0.5 mg.) produce a fall; larger doses, usually a rise in blood pressure. However, the relative dose varies from subject to subject, that is, 1.0 mg. may cause a fall in one and a definite rise in another patient. A smaller dose in the latter will produce a fall. The heart rate, on the other hand, consistently shows a fall, irrespective of the behavior of the blood pressure.

DISCUSSION

Dale, in 1906, first postulated that ergot alkaloids produce firstly a specific paralysis of the sympathetic motor elements which adrenaline stimulates, and secondly a stimulation of plain muscular organs. It was Rothlin[28,29] who later could demonstrate that inhibitory, adrenergic functions of the sympathetic pathways are paralyzed as well. We have, therefore, to assume that ergot paralyzes all adrenergic function. Until recently, all available ergot preparations, except ergobasine which is purely oxytocic, contained both these ergot components. The effect of ergot alkaloids on the peripheral circulation, therefore, was inconstant and rather complex on account of the conflicting actions of the two constituents, that is, vasoconstriction and vasodilatation competing with each other. By analyzing the effect of the drugs before and after sympathectomy, we could demonstrate that the sympathicolytic action is dependent upon the integrity of the sympathetic pathways. In the sympathectomized limb, dilatation is no longer obtained and the direct pharmacologic action on plain muscular organs reveals itself in its pure form. It could be demonstrated that in the sympathectomized limb ergotamine tartrate produces a marked reduction in the peripheral blood flow, as judged by the plethysmogram. Our results, therefore, confirm those already reported in human subjects by various other authors, except, perhaps, that our results in contrast to the earlier investigations[42] have been quantitative as well as qualitative. Graham and Wolff[15] have demonstrated that the effect of ergotamine tartrate in cases of migraine results from the vasoconstrictor action of the drug on the cranial arteries. They found that the skin temperature changes with small doses only, that the pulse rate

declines by about 18 per cent, and that there is a rise in blood pressure of about 20 per cent. Their results confirm those of Pool and co-workers,[27] von Storch and Meritt,[43] and Lev and Hamburger.[24]

It was the possibility of eliminating the direct pharmacologic action on smooth muscle of ergotamine and of producing a drug with a purely sympathicolytic effect which led Stoll and Rothlin to develop new ergot derivatives. Rothlin[30,31] and Rothlin and Bruegger[33] could demonstrate in animal experiments that hydrogenation of the ergot alkaloids produces this increase in sympathicolytic effect, and at the same time, reduces the action on smooth muscle. The few clinical results so far available as to the effect of the hydrogenated ergot derivative, dihydroergotamine, seem to confirm this. Hartman[16] gave the drug to twenty patients intramuscularly and found no demonstrable effect on the pulse rate, the blood pressure, the pulsations in the radial, the dorsalis pedis, and posterior tibial arteries, or in the color and temperature of the skin of the extremities. Exactly the same results were reported by Horton and associates.[17] Imfeld,[18] on the other hand, speaks of vasodilatation in cases of Raynaud's phenomenon, intermittent claudication, thromboangiitis obliterans, angina pectoris, and acrocyanosis. However, the circulation in most of his cases was evaluated by the clinical picture only. His dose was 1.0 to 2.0 mg. subcutaneously and 1.0 mg. intravenously; he observed a fall in blood pressure in one person, no effect in two, and a rise in four of his subjects. Rothlin,[30] Stoll,[36] Bruegger,[6] Rothlin and Bruegger,[33] Imfeld,[18] and Spühler[35] all hold that dihydroergotamine has hardly any, or even no effect whatsoever, on smooth muscle. The effect on the peripheral circulation in man has, however, never been critically analyzed with sensitive, quantitative methods. Using the Goetz plethysmographic method, we demonstrated that dihydroergotamine, like its original compound, ergotamine, will diminish the peripheral blood flow in the sympathectomized limb. It is, therefore, certain that dihydroergotamine still contains the direct pharmacologic action on smooth muscle and is not a purely sympathicolytic drug. However, vasoconstriction from dihydroergotamine is less pronounced and apparently less lasting than from the original compound, ergotamine tartrate. We know from the experiments of Graham and Wolff[15] that the effect of ergotamine is due to the vasoconstrictor action of the drug on the cerebral vessels. Spühler[35] has pointed out that dihydroergotamine is a very powerful drug in relieving migrainous headache, and it may be that it is the vasoconstrictor component still present in dihydroergotamine which is responsible for this beneficial effect. In contrast, in none of our patients did dihydroergocornine reduce the blood flow in the sympathectomized limb and in the normally innervated limb, the only reaction so far recorded has been vasodilatation. Dihydroergocornine, therefore, does not contain the direct action on the blood vessels so characteristic of the other ergot alkaloids and its action is purely sympathicolytic.

Although our results concerning the effect of dihydroergotamine on smooth muscle do not substantiate the clinical observations of the various workers, they are supported by experiments in dogs reported by Horton and associates.[17]

These authors found that in the dog dihydroergotamine is a vasoconstricting agent similar to ergotamine tartrate, but that the effects of dihydroergotamine are of shorter duration than those of the latter ergot preparation. They write that additional observations on man tended to confirm this. Our results definately prove that in man the action of dihydroergotamine is still characterized by the two active principles found in the original alkaloid, ergotamine tartrate. Dihydroergocornine, on the other hand, is the only drug which has a purely sympathicolytic effect.

The sympathicolytic effect finds further expression in the plethysmogram; it has been demonstrated by numerous authors that the plethysmogram of the normal individual does not present a straight line but shows marked spontaneous fluctuations, vasoconstriction alternating with vasodilatation. These fluctuations are generally accepted as the result of impulses which are transmitted from the vasomotor centers to the blood vessels. As Goetz[13] has demonstrated, they are dependent on the integrity of the sympathetic nervous system and they reflect the rhythmic nature of central sympathetic vasomotor activity. Following sympathectomy, these fluctuations are no longer recorded.[13] The effect of ergot derivatives on these spontaneous fluctuations of the plethysmogram was first investigated in Basle* with the plethysmographic method of Rothlin and Bluntschli.[32] It was then demonstrated that following 1.0 mg. of dihydroergotamine or ergotamine tartrate the spontaneous fluctuations in the plethysmogram may entirely disappear. During the present investigations a similar disappearance of the spontaneous fluctuations has often been observed in normally innervated limbs following the injection of dihydroergocornine. This may be claimed as evidence that there is, to say the least, interruption of conduction of sympathetic impulses and possibly paralysis of central vasomotor activity. The disappearance of the spontaneous fluctuations in the plethysmogram following sympathectomy and following the administration of the sympathicolytic component of ergot led us to investigate the action of these sympathicolytic derivatives.

Dale ascribed the action of the component which produced "specific paralysis of the motor elements in the structures associated with sympathetic innervation" in his drugs to paralysis "of the sympathetic motor myoneural junctions in the arterial walls." We could demonstrate that in the normally innervated limb the sympathetic inhibitory (vasodilator) effect of ergotamine tartrate and dihydroergotamine is opposed by the direct-acting vasoconstrictor principle, and the effect on the peripheral circulation, therefore, is characterized by the interaction of both these principles, vasodilatation competing with vasoconstriction. In the sympathectomized extremity, however, the effect of both drugs is invariably marked vasoconstriction. The fact that the vasodilator component of ergotamine tartrate and dihydroergotamine seen in the normally innervated limb is abolished by preganglionic sympathectomy suggests, but does not prove, that its action is not on the sympathetic myoneural junction but that the sympathicolytic effect is dependent on the integrity of the sympathetic path-

*Unpublished data.

ways and that the sympathicolytic principle acts over higher nervous mechanisms. There is no reason to assume that there is a different mechanism in the case of the sympathicolytic effect of dihydroergocornine. Investigations concerning blood pressure changes after dihydroergocornine in cases of high transverse spinal lesions and following splanchnicectomy led us,[5] in fact, to place the site of action in the medulla and/or hypothalamus.

This, to our knowledge, is the first time that it has been demonstrated that an ergot derivative acts in a purely sympathicolytic fashion in man. The possibility of therapeutic application in cases of pathologic spasm, such as Raynaud's phenomenon, acrocyanosis, and similar vascular disorders or in organic vascular diseases with superadded spasm such as embolism or in some cases of thromboangiitis obliterans, suggests itself and will be the subject of further investigations. The sympathicolytic effect of the drug has already been tested in cases of hypertension, where hyperactivity of the sympathetic nervous system has been blamed by many authors as at least a factor in maintaining the elevated arterial blood pressure. The results obtained in cases of hypertension have been reported elsewhere[5] and indeed, in all cases of essential hypertension, dihydroergocornine caused a fall in blood pressure which in some was extremely prolonged.

SUMMARY AND CONCLUSIONS

The effect of two new hydrogenated derivatives of ergot (dihydroergotamine, referred to as DHE 45, and dihydroergocornine, referred to as DHO 180) on the cardiovascular system was investigated in twenty-four subjects and their action compared with that of ergotamine tartrate (Gynergen), with particular reference to their respective sympathicolytic properties.

It could be demonstrated, by using an accurate, quantitative method, that both ergotamine tartrate and dihydroergotamine contain the two components of ergot originally described by Dale, that is, the direct (constrictor) action on plain muscular organs and the sympathetic inhibitory (vasodilator) principle. Their effect in the normally innervated limb, therefore, is complex, due to the interaction of these two opposing elements which, however, could be separated by investigating the effect of the drugs in cases who had undergone preganglionic sympathectomy. It could be demonstrated that following sympathectomy the sympathicolytic effect (vasodilatation) can no longer be registered and that in the sympathectomized limb both ergotamine tartrate and its dihydrogenated derivative are pure vasoconstrictors. The sympathicolytic component, therefore, is dependent on the integrity of the sympathetic pathways, and dihydroergotamine is not a derivative of ergot with a purely sympathicolytic action, as has been reported by various authors.

Dihydroergocornine, in contrast, does not produce any constriction in the sympathectomized limb, and since it produces dilatation in the normally innervated limb, it has to be regarded as the first known ergot derivative which acts in a purely sympathicolytic fashion in man. The fact that the sympathicolytic principle is dependent on the integrity of the sympathetic pathways suggests

that it does not act peripherally on the sympathetic myoneural junction but over higher sympathetic centers.

Mention is made of evidence presented elsewhere that the site of action of the sympathicolytic principle of dihydroergocornine has, in fact, to be looked for in the medulla and/or hypothalamus.

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TERMINAL ELECTROCARDIOGRAPHIC PATTERNS IN EXPERIMENTAL ANOXIA, CORONARY OCCLUSION, AND HEMORRHAGIC SHOCK

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IN RECENT years, many experiments in this laboratory have provided electrocardiographic and other observations which furnish data upon the alterations in activity in mammalian hearts approaching death. Clinical papers reviewed in the concurrently published paper by Stroud and Feil[16] have described the alterations of activity in dying human hearts. The fortuitous, naturally occurring changes in conditions within the organism leading to cessation of cardiac activity in human cases are not as well known to the observer as are the planned changes in the condition of the animal in well-controlled experiments. An analysis of the experimental observations may aid in discovering patterns in cardiac activity in the final stages which will contribute to better interpretation of events observed in human hearts.

The changes in the physiologic activity which are of major interest and importance in dying hearts of experimental animals are those which are observed during the time when effective pumping action is ceasing in cases of gradual cessation, or during the development of ventricular fibrillation in cases that cease suddenly via fibrillation. Changes that occur after the heart has ceased to eject blood and maintain a peripheral blood pressure do not contribute to the death of the organism. In a tabulation and discussion of modes or patterns of cardiac death, therefore, care should be taken to exclude observations which would lead to false conclusions. For example, some hearts that have stopped due to pacemaker failure or conduction failure develop a sluggish ventricular fibrillation after a period of many seconds of standstill or after extreme slowing with only an occasional ineffectual beat and with the blood pressure near zero. Such a case is not a fibrillation death, but a death from failure of the pacemaker or of the conduction system, together with weakening of the cardiac muscular contractions.

Some of the observations to be reported were compiled from the records of experiments which were performed by several investigators in our laboratory[7,9,12] for the study of cardiac and circulation problems other than the cardiac

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approach to death. Other experiments were planned for specific quantitative study of phenomena associated with cardiac failure, especially in relation to ventricular fibrillation.[5,6,10,19]

PROCEDURES

Dogs were used in all experiments. They were anesthetized with sodium barbital, some having preanesthetic doses of morphine.

The anoxia experiments were of two kinds: (1) with opened chests and artificial respiration, and (2) with unopened chests and natural respiration. The experiments with opened chests were performed for the primary purpose of studying the effects of anoxia upon myocardial action potentials as recorded from local contiguous bipolar leads.[7] Observations upon the terminal changes in electrocardiograms were of secondary concern at the time, but these experiments now afford an opportunity to compare the results of anoxia combined with major surgical trauma with the effects of anoxia with little surgery. Furthermore, the animals with opened chests were unable to change the ventilation rate as anoxia developed. The artificial respiration was adjusted before rebreathing was begun to provide just sufficient overventilation to prevent any spontaneous respiratory movements while being ventilated with air with normal oxygen content. Some hyperpneic movements developed as the oxygen content of inspired air was lowered. The animals with unopened chests developed considerable hyperpnea.

Respiratory apparatus for the experiments with opened chests consisted of a large respirometer tank with an external circuit including a soda lime cartridge. The air was circulated and forced into the dogs' lungs intermittently by a piston pump. By recirculation and rebreathing the air, its oxygen content was gradually reduced. The apparatus has been illustrated and described in detail elsewhere.[7]

In the experiments with unopened chests, the animals rebreathed air from the large recording respirometer of Burlage and Wiggers, which was described recently by Randall.[12] In both kinds of anoxia experiments the percentage of oxygen in the tank could be determined, approximately, from a scale on the apparatus. Exact checks were made frequently by analyzing air samples with the Henderson-Orsat apparatus.

The coronary occlusion experiments were performed as described by Harris and Guevara Rojas.[6] In all experiments to be included in this presentation the anterior descending artery was clamped.

The production of hemorrhagic shock was accomplished by a standardized technique developed by Wiggers and Werle.[20] This consists of carefully graded and timed stages of hemorrhagic hypotension as follows: ninety minutes with mean arterial pressure kept at approximately 50 mm. Hg, and forty-five minutes at about 30 mm. of mercury. These levels are produced and maintained by repeatedly drawing the amounts of blood that are required. At the end of the prescribed hypotension periods all of the withdrawn blood is reinfused. After recovery of the control arterial pressure level, the pressure again typically goes into decline and the animal dies in shock in about five to seven hours after the reinfusion. This paper describes the cardiac behavior in the last stages of pumping. Earlier electrocardiographic changes in hemorrhagic shock have been described elsewhere.[9]

RESULTS

Anoxemic Anoxia.—The final changes leading to cessation of pumping in hearts exposed to gradually lowered oxygen tensions exhibit several different patterns, all of which are due to failure of the pacemaker or of conduction, or both.

In Animals with Closed Chests: The series of illustrative records to follow were taken from experiments in which the chests of the animals were left intact. Fig. 1 is a record from an animal that had been subjected to a reduced oxygen tension for almost six hours. The reduction was slow. During the first forty minutes of rebreathing, the oxygen content of the tank was dropped to 10 per cent. During the next one and one-half hours it was slowly decreased to 8.8 per cent, after which it was kept near 8 per cent for about two additional hours. After this there was a slow decline until failure occurred. The final analysis showed an oxygen concentration of 5 per cent.

The record presents a case of total heart block, the P waves and QRS-T complexes showing complete dissociation at this stage. The vagus nerves had been sectioned earlier in the experiment. Therefore, the conduction failure manifest must be regarded as an intrinsic failure of function in the specialized A-V conducting tissue. This failure occurred when the mean arterial pressure had dropped to about 25 mm. of mercury. Respiration had stopped a few seconds before the block occurred. During the latter part of the period of hypotension leading to block, there had been gradual slowing of the cardiac rate and lengthening of the P-R interval from the original 0.10 second to 0.22 second after which dissociation occurred.

Fig. 2 is from another animal in the terminal stage of a long severe anoxia. It shows failure of A-V conduction with the ventricles remaining in standstill. In Fig. 2, *A* may be seen the stage just preceding the A-V conduction failure. At this point the P-R interval had increased from the control duration of 0.10 second to about 0.25 second.

Fig. 2,*B*, taken a short time afterward, shows that only the auricles are continuing to beat. It may be inferred that in this case anoxic depression of the A-V node and other possible ventricular pacemakers prevented the establishment of an idioventricular rhythm. At the time that the long P-R intervals and conduction failure were recorded, this animal had been in severe anoxia (below 7 per cent) for more than three hours. It is unusual that an animal will live so long at this level. Ordinarily in our experiments about 8 per cent was the limit for survival for periods extending into hours.

Fig. 3 shows another pattern of cardiac approach to cessation in milder anoxia of longer duration. In Fig. 3, *A* the pacemaker suddenly ceased to discharge. Fig. 3, *B* shows the very slow ventricular rhythm which was established for a short time. Just before the pacemaker stopped the rate was 125 per minute which is quite normal for anesthetized dogs, though in this case it represented a relatively great slowing from the rate of 200 to 225 which had prevailed for the last several hours of this twelve-hour experiment. At the time the pacemaker ceased discharging there was no evidence of deterioration of A-V conduction.

The oxygen concentration in the tank at the end was 9.4 per cent. It had not been below this level at any time. Tolerance to a lack of oxygen varies appreciably in different dogs.

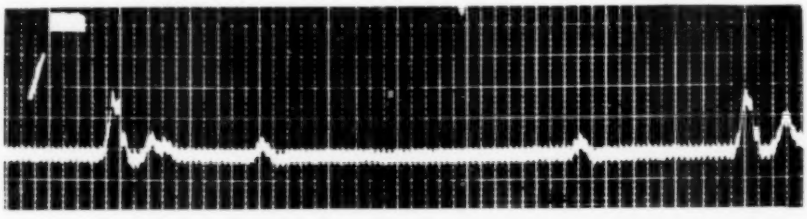

Fig. 1.—Lead III of an electrocardiogram showing complete heart block in a dog with heart failing in severe anoxia. Note abnormal width of QRS, signifying impairment of intraventricular conduction.

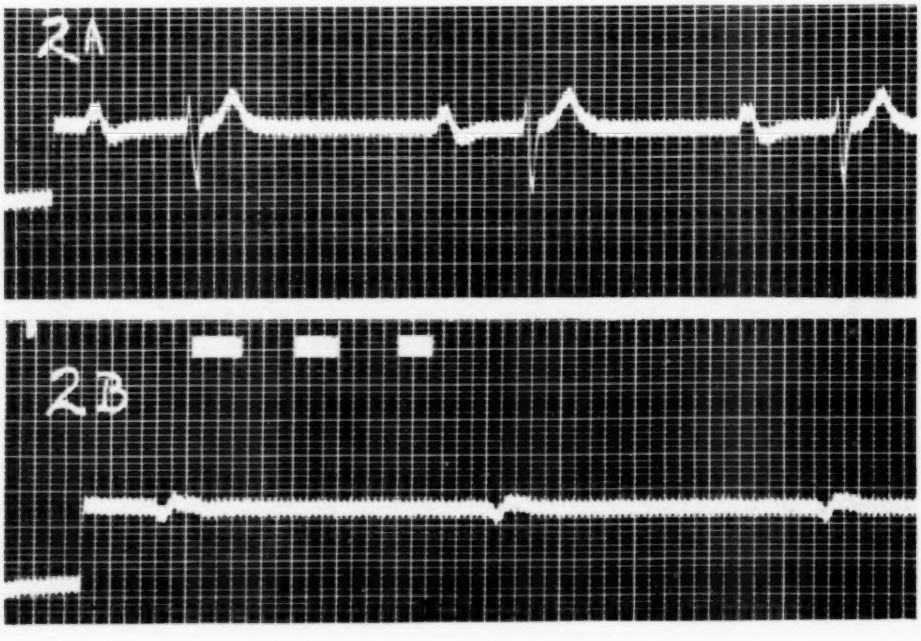

Fig. 2.—Failure of A-V conduction with ventricular standstill, the auricles continuing to beat, in an anoxic dog. *A* shows greatly prolonged P-R intervals, *B*, taken a few seconds later, contains P waves only.

Fig. 4 is from an anoxia experiment in which cardiac action was brought to an end via gradual pacemaker slowing and stoppage, followed by a period of A-V nodal rhythm. This experiment lasted more than six hours. The record is from the third and last period of rebreathing to deep anoxia in this experiment. During the greater part of the experiment and during the last rebreathing trial until five minutes prior to the time that the record shown in Fig. 4, *A* was made, the heart rate varied between 150 and 170 per minute. During that last preceding five

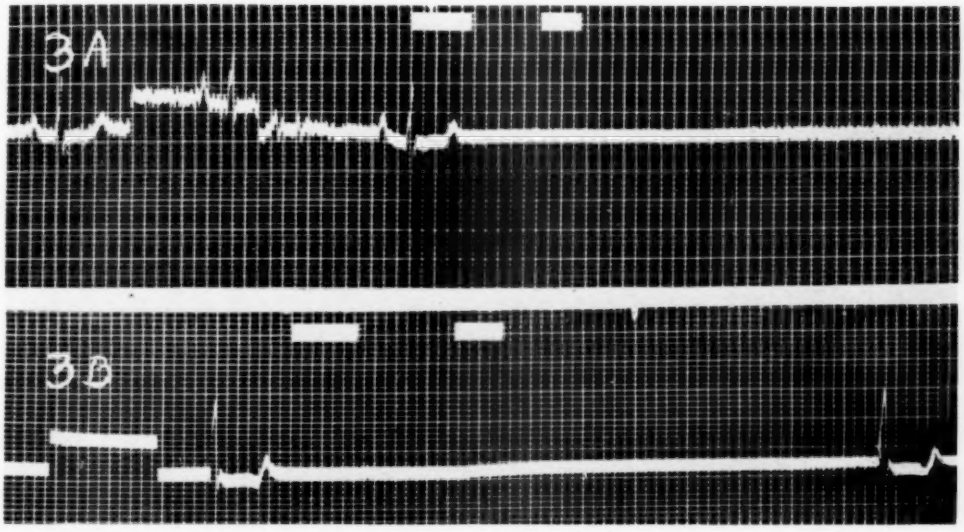

Fig. 3.—Sudden cessation of the pacemaker and development of slow idioventricular rhythm in heart of an anoxic dog. *B* was taken very quickly after *A*.

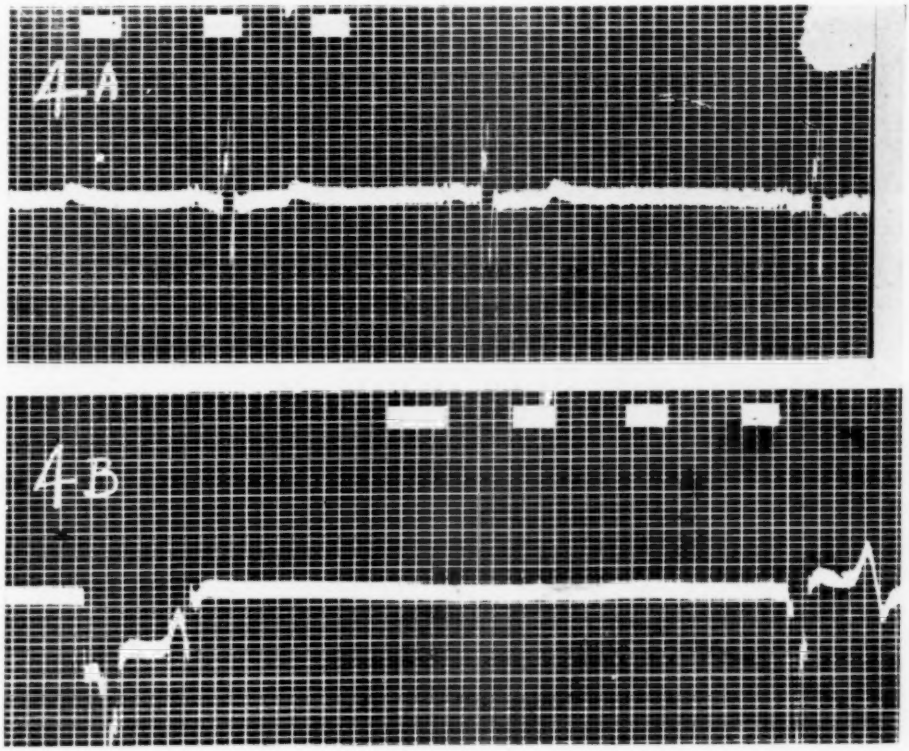

Fig. 4.—Gradual cessation of pacemaker followed by ventricular rhythm in an anoxic dog. *B* follows quickly after *A*.

minutes the rate fell to that shown in the record (about 40), and the auricles stopped very soon thereafter. The P-R intervals were normal (0.09 second) until the pacemaker stopped. Fig. 4, *B* shows the slow A-V nodal rhythm which followed for a minute or two before the ventricles stopped.

Of twelve animals with unopened chests which died after periods of slowly developing anoxia, independent rhythms of auricles and ventricles developed before the end in three, ventricular standstill with auricular continuation in one, very slow pacemaker and long P-R (end not recorded) in one, pacemaker failure with subsequent A-V nodal rhythm in six, and ventricular fibrillation in one.

Summarizing, there were four cases of conduction failure, six cases of pacemaker failure, one case in which conduction and the pacemaker were failing simultaneously, and one questionable case of ventricular fibrillation.

In Animals With Open Chests: In the experiments with exposed hearts and artificial respiration, the patterns of terminal activity were very similar to those already described. These changes in seven consecutive experiments as read from electrocardiograms are summarized in Table I.

TABLE I. TERMINAL CARDIAC CHANGES IN ANOXIA IN ANIMALS WITH OPEN CHESTS AND ARTIFICIAL RESPIRATION

EXP. NO.	SEQUENCE OF TERMINAL CHANGES
1	Great slowing simultaneously with long P-R; standstill, no nodal rhythm
2	Slow pacemaker and long P-R; end not recorded
3	Same as *1*
4	Slight slowing with normal P-R; pacemaker stopped; nodal rhythm; complete standstill
5	Same as *2*
6	Extreme slowing with normal P-R; pacemaker stopped; no nodal rhythm
7	Slowing; normal P-R; pacemaker failure; nodal rhythm

Four of these seven experiments (Numbers 1, 2, 3, and 5) exhibited simultaneous deterioration of function of the pacemaker and the conduction system. In the other three, the pacemaker failed while there was as yet no evidence of conduction deficit. These results may be regarded as identical with those from animals with unopened chests and natural respiration.

The termination of pumping activity has now been observed in more than sixty hearts dying in anoxia. Electrocardiograms have not been made in all animals with open chests, but the hearts of these animals have been observed visually. Of this large number, only one stopped in ventricular fibrillation. Many have developed sluggish fibrillary movements after an interval of total standstill following pacemaker stoppage or ventricular standstill signifying conduction failure. Considering all of the evidence from anoxic animals with opened and unopened chests, there appears to be no sound basis upon which to predict that in generalized anoxia the pacemaker will fail before conduction, or vice versa. When one fails, failure of the other is near. Stoppage via ventricular fibrillation is rare in anoxic deaths. De Somer[15] stated that during fatal asphyxiation the P

wave disappears first, that is, pacemaker standstill. The sequence is, therefore, similar to that seen in about one-half of our anoxia cases.

Vagal Effects in Anoxia: The question of vagal effects in anoxia has been considered. Fig. 5 was taken from an experiment showing vagal slowing and A-V conduction block. When this record was made the arterial pressure was still normal (mean 100 mm. Hg) and the ventricles appeared vigorous. As the blood pressure declined following the stage illustrated, an interesting series of further changes occurred. At about 50 mm. Hg the auricles stopped and A-V nodal rhythm supervened for a short time. The auricles returned to activity at 30 mm. and the normal excitation sequence, with slowing rate, was observed until the pacemaker failed at about 20 mm. of mercury. Then the whole heart remained in standstill. The early block, slowing, and disappearance of P were in all probability due to vagal influence, but the pacemaker stoppage at low pressure was not. This animal had been exposed to moderate anoxia (12 to 8.5 per cent oxygen) for about the first seven hours of the experiment and to room air for two hours and forty-five minutes. After that rebreathing from the tank air (then 8.7 per cent oxygen) was started again and the reduction was allowed to continue without interruption until failure occurred about twelve minutes later. The final air sample contained 6.0 per cent oxygen. The records of vagal effects, and subsequent events of failure that were described, all occurred during the last five minutes preceding standstill.

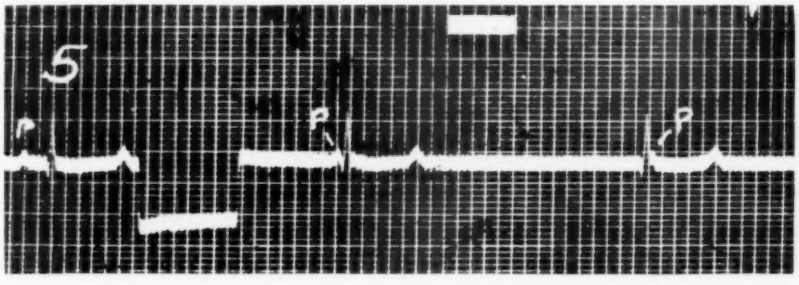

Fig. 5.—Heart block due to vagal influence in anoxic dog with well-maintained blood pressure.

In certain other experiments exhibiting slowing of the rate or block while the blood pressure was well above levels associated with failure (70 to 100 mm. Hg), the vagus nerves have been sectioned. These hearts have then resumed a rapid rate with normal pacemaker action and normal A-V conduction. Therefore, the disturbances in pacemaker function and in A-V conduction that occur in severe anoxia while the blood pressure remains high are inferred to be due to vagal impulses. However, cardiac disturbances of similar electrocardiographic appearance have been observed to occur after the blood pressure had fallen to the region of 30 mm. Hg and below, with and without intact vagus nerves. These terminal changes must be considered as due to the effects of oxygen lack in the cardiac tissues.

Long continued exposure to low oxygen concentration is not necessary to the exhibition of vagal effects. In fact, they occur much more regularly in cases of rapidly induced anoxia. In the experiments of Greene and Gilbert,[5] who gave a good description of vagal effects in anoxia and differentiated between the vagal and nonvagal stages of slowing and block, the stage of complete cardiac failure was reached in about fifteen minutes. In the long continued experiment which has been described it is possible that only the last twelve minutes (when, following two hours on room air, the concentration was rapidly reduced to 6.0 per cent) have an important relation to the vagal effects. Experiments with intact vagi in which the initial slow rebreathing was carried to a more severe level (about 8 per cent oxygen) and maintained at that level for periods of one to three hours have usually not exhibited pacemaker slowing or conduction disturbances with relatively well-maintained blood pressure which are considered evidences of vagal activity.

The consensus of evidence indicates that the central cells of the cardioinhibitory mechanism may be excited (directly or reflexly?) by rapidly developed oxygen lack, and are less likely to show appreciable excitation in a very gradually developed severe anoxic state.

Coronary Occlusion.—In our studies of coronary occlusion, the only route to failure of pumping which was recorded and studied was ventricular fibrillation. In those experiments the aim was to analyze the process of initiation of ventricular fibrillation as it occurs in coronary occlusion. A description of the changes in the action of the heart as they develop minute by minute in experimental coronary occlusion has been published elsewhere.[6] It should be sufficient here to point out only the major changes in activity. In a typical experiment the closing of the clamp on the anterior descending artery is followed by the development of ventricular ectopic systoles. The ectopic beats begin within two or three minutes of occlusion as single complexes and within another minute or two change to short runs of two or three. The groups continue to grow more frequent and become longer until, in a final paroxysm, the frequency of the ectopic discharges accelerates until coordinated activity breaks down into ventricular fibrillation. The period between occlusion and fibrillation varied between one minute, twenty seconds and nine minutes. Eighty per cent of the fibrillations (twenty out of twenty-five) occurred within the first five minutes of occlusion. In trials which did not lead to fibrillation the frequency of ectopic discharges passed through a maximum at about four to five minutes and then declined, sometimes stopping entirely by the tenth minute of occlusion.

To expedite many of the later experiments, the occluding clamp was left on the artery for periods of only ten to twenty minutes if fibrillation did not occur earlier, and then removed. After a recovery period of thirty minutes the test was repeated. If fibrillation did occur the clamp was removed immediately and the ventricles were defibrillated by use of the alternating current defibrillator. Usually it was possible to defibrillate the ventricles of the same heart repeatedly. The number of repetitions that were possible during a day's experiment varied up to a maximum of seven. In some trials, ventricles which did not fibrillate during

the period of occlusion went into fibrillation upon removal of the occluding clamp. In such cases the fibrillation occurred within a period of about one minute after opening the clamp. If a period as long as one and one-half minutes passed without fibrillation there was no further danger that fibrillation would develop. Defibrillation was difficult in these coronary occlusion experiments. Often the ventricles had to be defibrillated several times after one trial because the conditions which produced fibrillation were still present and caused immediate return to fibrillation. If, upon defibrillating, the heart remained out of fibrillation for two minutes it was generally safe from spontaneous refibrillation.

After the hearts had been weakened by repeated periods of occlusion, fibrillations, and defibrillations, they usually died in standstill by pacemaker failure and conduction failure, as in anoxia.

No dog's heart has been observed to recover from ventricular fibrillation spontaneously. Without the defibrillator each fibrillation would have been a fibrillation death.

The results of all of the occlusion trials are summarized in Table II. During occlusion of the anterior descending artery there were twenty-five fibrillations in fifty trials. Of the twenty-five trials with failures to fibrillate during occlusion, there were four fibrillations upon release of the clamp. There were, therefore, a total of twenty-nine fibrillations resulting from fifty occlusions and releases. Fibrillation occurred in 50 per cent of the trials if the occlusion periods alone are considered and in 58 per cent of trials if the fibrillations upon release are included also.

In experiments upon fourteen dogs, fibrillation occurred in nine during occlusion in one or more trials. Of the five hearts that did not fibrillate during occlusion, fibrillation occurred in two upon removal of the clamp. In three there were no fibrillations during occlusion or upon release. In five there were no failures to fibrillate during occlusion.

One of the animals in which fibrillation failed in all trials was very deeply anesthetized by an overdose of sodium barbital. This may possibly be a clue to the reason for absence of fibrillation in this case. If the deep anesthesia depressed irritability, thereby preventing the generation of ectopic systoles, then fibrillation would not be expected (see discussion). No reason can be offered for the failures in the other two animals in which no fibrillation occurred.

In the coronary ligation experiments of Smith[14] ventricular fibrillation occurred much less often than in the results which have just been described. Upon ligation of the anterior descending artery in eleven dogs there was ventricular fibrillation in only one. There were two ventricular fibrillations in fourteen ligations of the left circumflex artery. Wood and Wolferth[21] indicate a higher incidence of ventricular fibrillation upon occlusion of either of the main branches of the left coronary artery. It is possible that the kind of anesthesia used makes a significant difference in the tendency to ectopic ventricular systoles and fibrillation. In our experiments and in those of Wood and Wolferth, barbiturates were used. Ether anesthesia was used by Smith.

In the one monkey heart that was used there were no fibrillations during the four occlusion periods. However, fibrillation occurred upon three of the four releases. Upon the basis of only one experiment no comparison of monkey and dog hearts can be made.

TABLE II. VENTRICULAR FIBRILLATIONS AND FAILURES TO FIBRILLATE DURING OCCLUSION AND AFTER RELEASE OF THE ANTERIOR DESCENDING ARTERY

EXP. NO.	DURING OCCLUSION		RELEASE	
	FIBRILLATION	FAILURE	FIBRILLATION	FAILURE
1	0	1	1	0
2	3	2	1	1
3	2	0		
4	5	2	1	1
5	1	0		
6	2	2	0	2
7	2	0		
8	0	2	0	2
9	0	4	0	4
10	1*	0		
11	7	0		
12	0	6	1	5
13	0	5	0	5
14	2	1	0	1
Total	25	25	4	21
On a monkey	0	4	3	1

*After this fibrillation resulting from occlusion, there were repeated spontaneous fibrillations which rendered further trials impossible.

Hemorrhagic Shock.—The final phase of pumping action in the hearts of animals dying of hemorrhagic shock has been studied from electrocardiograms correlated with kymograph records of mean blood pressures.[9] Fig. 6 is a record of terminal activity in an experiment that illustrates a frequently occurring pattern. The tracing shown in Fig. 6, *A* was made during the transition from normal S-A nodal rhythm to A-V nodal rhythm. It shows brief intermittent periods of failure of the S-A pacemaker with substitution of an ectopic one in the A-V node or bundle of His and recoveries for brief periods of activity of the S-A pacemaker. Such transitional shifting of pacemakers lasted for perhaps two or three minutes

(electrocardiographic records were not continuous) and then the S-A pacemaker stopped for the last time. The record shown in Fig 6, *B* was made shortly after the final cessation of the S-A pacemaker and that in Fig 6, *C*, less than one minute later. At the time that Fig. 6, *A* was recorded, the mean blood pressure was about 22 mm. Hg and falling. When Fig. 6, *C* was recorded, the pressure was near zero. In this series of nine hemorrhagic shock experiments with frequent electrocardiograms, seven cardiac deaths occurred with pacemaker stoppage and subsequent A-V nodal or idioventricular rhythm characterizing the final stage of pumping activity. The P-R intervals were normal up to the time of pacemaker failure in all cases. One experiment was terminated by ventricular fibrillation. The final record from the other animal showed a very slow rate while maintaining a normal A-V sequence. It probably stopped in pacemaker failure as did the seven others mentioned here. Blood pressure readings in the different experiments at the time of the occurrence of pacemaker failure and the beginning of nodal rhythm varied from 40 to less than 20 mm. of mercury. In six experiments, the pressure was 30 mm. or less. The one fibrillation occurred at a pressure of 20 mm. of mercury.

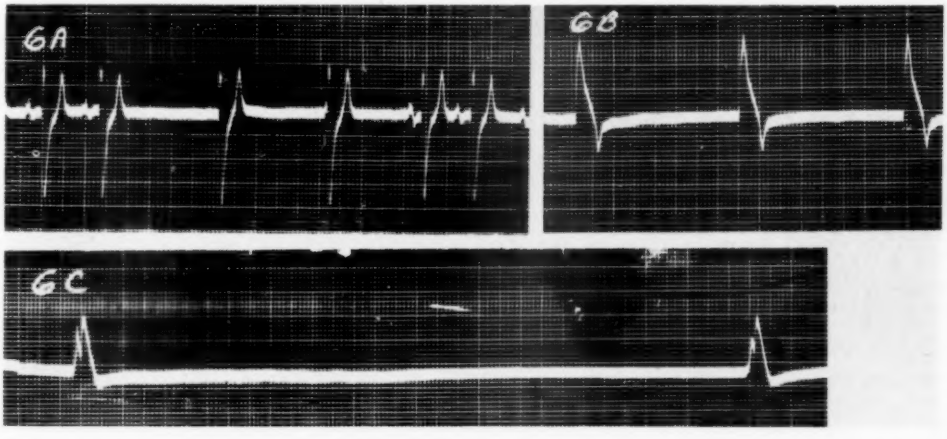

Fig. 6.—Cessation of pacemaker action, development of idioventricular rhythm, and final slowing in dog in the terminal stages of hemorrhagic shock. *A*, Intermittent periods of normal pacemaker and ventricular pacemaker rhythms. *B*, Ventricular pacemaker only. *C*, Great slowing just before standstill.

It must be borne in mind that these failures did not occur upon the mere reduction of mean arterial pressure to the region of 30 mm. of mercury. They occurred as terminal events in hemorrhagic shock. During the standard procedures to produce hemorrhagic shock earlier in each experiment, the arterial pressure was kept at about 30 mm. Hg for a period of forty-five minutes. During this time there was no evidence in any case of impending pacemaker or other cardiac failure. Hours later, upon the redecline of arterial pressure, the described changes occurred as parts of the shock syndrome.

In experiments by Negovski,[11] with rapid exsanguination to the point of clinical death, the terminal electrocardiograms show periods of intermittent pacemaker action and failure followed by pacemaker standstill and nodal rhythm. This sequence is identical to that seen in the terminal phase of hemorrhagic shock here. Since rapid exsanguination to 30 mm. Hg in our laboratory does not produce pacemaker failure, it is probable that in Negovski's experiments stoppage occurred after lower pressure levels were reached. Ventricular fibrillation is not mentioned in the exsanguination experiments of Negovski.

DISCUSSION

This study emphatically points out the great difference in the frequency of occurrence of ventricular fibrillation in experimental coronary occlusion as contrasted with general anoxia or hemorrhagic shock. The reasons for this difference are to be found in studies upon the nature of ventricular fibrillation[2,18] and the changes in the activities and properties of cardiac muscle which initiate fibrillation.[6,10]

The consensus of experimental evidence indicates that ventricular fibrillation is continuous, irregular, incoordinate, circuitous excitation and re-excitation of the various portions of the ventricular myocardium. In normally beating ventricles, circuitous re-excitation is prevented by the refractoriness of the muscle. In the dog heart the duration of the refractory period of a given small fraction of the myocardium (R-T interval of a local response) during a normal beat is about 0.18 to 0.20 second, while the period required for conduction of the excitatory process throughout the ventricular musculature (duration of QRS) is about 0.03 to 0.04 second. In a single ventricular ectopic systole induced in a normally beating heart, the period of conduction through the ventricles is about 0.05 to 0.07 second, or considerably less than one-half the duration of refractoriness. To make re-entrant excitation possible, therefore, it is necessary that the period of refractoriness be shortened markedly or that conduction be greatly slowed, or both. It has been shown[10] that rapid repetitive ectopic systoles bring about both of these changes, and that if artificial stimuli are applied to the ventricles in a suitable accelerating sequence they will produce fibrillation, though the intensity of the individual shocks be but little more than the threshold for a diastolic premature systole.

Short direct current stimuli applied during the vulnerable period,[10,19] direct current stimuli (especially anodal) of several seconds' duration,[5] and coronary occlusion[6] all produce ventricular fibrillation. By all of these methods the fibrillation is preceded by a repetitive and accelerating train of ectopic systoles from a discharging focus, or multiple foci in coronary occlusion. When the acceleration reaches the state that the interval between ventricular complexes of the electrocardiogram or of spikes from local leads is shortened to about 0.08 second, coordinated activity disappears and the ventricles enter the state of fibrillation.

This description of the changes that initiate fibrillation offers an explanation for the findings that a condition which produces accelerating groups of ectopic

systoles (coronary occlusion) causes fibrillation in a high percentage of trials, whereas conditions which ordinarily do not produce ectopic discharges only rarely produce fibrillation.

By multiple local leads recorded simultaneously, it has been shown that the ectopic discharges which are characteristic of coronary occlusion arise in the boundary between ischemic and nonischemic muscle and that very high spike voltages can sometimes be recorded there.[6] The logical interpretation is that electrochemical gradients in this zone give rise to the discharge of impulses. In overall anoxia and in hemorrhagic shock there is no such boundary. The fundamental cause of the ectopic discharges which occur for a brief period after *removing* the clamp from the artery to an ischemic area has not been determined. It appears possible that boundaries with electrochemical gradients exist for a fleeting moment in the neighborhood of each small blood vessel in the ischemic muscle, thus producing a vast number of potential foci.

The terminal changes that have been recorded in overall anoxia were almost equally divided between initial failure of A-V conduction and initial failure of the pacemaker. Both may be regarded as manifestations of reduction of functional ability due to oxygen lack. The rhythmic cells of the S-A node are more vulnerable to anoxia than are the A-V node and bundle in some dogs, but the opposite relation was found in others, and in some, equal susceptibilities were observed. The difference is small and probably unimportant in all cases.

Pacemaker failure was the characteristic feature of cardiac cessation in animals dying of hemorrhagic shock. Auricular stoppage and the subsequent development of A-V nodal rhythm were observed in all animals subjected to hemorrhagic shock except in the one animal in which ventricular fibrillation developed. The greater susceptibility to functional damage of the pacemaker as compared with that of A-V conduction tissues appears to be a possible difference between the reaction of the heart to slowly developing general anoxia and the reaction to hemorrhagic shock.

Studies on human cardiac death from randomly reported causes reveal patterns of terminal activity which are strikingly similar to those seen experimentally. In the cases of Hanson and associates,[4] Sigler and co-workers,[13] Iwasaki,[8] and the accompanying paper of Stroud and Feil,[16] the first major electrocardiographic change often was cessation of P waves. This was preceded by a gradually slowing rate. In a large proportion of cases the pacemaker failure was followed by nodal or idioventricular rhythm for a short time before ventricular standstill occurred. Auriculoventricular conduction failure with dissociation was reported in four of twenty cases of Sigler and co-workers.[13] In one of these the terminal state resulted from a ruptured ectopic pregnancy; in two, from cerebral hemorrhage; and in one, from a bleeding gastric ulcer. Three cases of A-V dissociation were reported by Dieuaide and Davidson.[1] The authors of the latter paper stated that the terminal state probably was due to oxygen deficiency and carbon dioxide accumulation. All of their patients were victims of chronic cardiac insufficiency.

In the extensive tabulation of cases from the literature by Stroud and Feil,[16] about one-third of the cases are listed as fibrillations. However, in this list the feeble terminal undulations which occur in some hearts following pacemaker failure and which do not contribute to death were counted along with the bona fide ventricular fibrillations which led to death, making the number of fibrillations listed too high. At least four of the ten listed ventricular fibrillations of Hanson and associates[4] were of this kind, one of them being precipitated by adrenalin. Five of their apparently valid fibrillation deaths occurred in severe infectious disease and one was listed as of unknown cause. In some of the other papers, it is impossible to distinguish the real ventricular fibrillation deaths from cases with unimportant late terminal undulations. Tabulations of this kind, therefore, must be viewed with caution.

There are reports of ventricular fibrillation in phosphorus poisoning,[8] carbon tetrachloride poisoning,[16] mercury poisoning,[17] and in infectious diseases. We have no experimental counterpart for the ventricular fibrillations in poisoning and infectious disease but, in accordance with the mechanism of initiation of fibrillation discussed previously, a hyperexcitability of ventricular tissues produced by toxic agents might produce discharging ectopic foci, tachycardia, and fibrillation. Controlled studies on these subjects are needed.

SUMMARY

Electrocardiographic records of dog hearts at the stage of termination of effective pumping in experiments upon generalized anoxia, coronary occlusion, and hemorrhagic shock have been collected and studied.

In nineteen general anoxia experiments from which terminal electrocardiograms are available, pacemaker stoppage or cessation of A-V conduction was the first gross manifestation of cardiac failure detectable in electrocardiograms in each case except one. Ventricular fibrillation occurred prior to stoppage in one. Of these nineteen animals, there were twelve with intact chests and seven with chests open for study upon the heart muscle. In a larger series of anoxic dogs with open chests and direct observation of the heart, making a total of more than sixty animals, there have been no further deaths by ventricular fibrillation, all hearts having stopped via pacemaker and conduction failure. The frequency with which pacemaker failure preceded conduction failure, and vice versa, was approximately equal in the nineteen experiments with terminal records.

In occlusion of the anterior descending coronary artery there were twenty-five fibrillations during fifty occlusion trials, and four additional fibrillations upon releases of the occluding clamp. Fibrillation occurred, therefore, in fifty per cent of the occlusions, or fifty-eight per cent of trials if fibrillations upon release are included.

In nine hemorrhagic shock experiments seven hearts failed by pacemaker stoppage, another probably did also, and one stopped via ventricular fibrillation.

The experimental conditions which produce a gradual overall diminution in the functional capacity of the cardiac tissues without predisposition to ectopic

ventricular systoles produced failure of the pacemaker or of A-V conduction, but very rarely induced ventricular fibrillation. The experimental condition (coronary occlusion) which predisposes to trains of ectopic ventricular systoles produced a high percentage of ventricular fibrillations. The reasons are discussed.

Observations in a few representative clinical papers are reviewed and compared with the experimental observations. Considerable agreement with the experimental patterns and with the conclusion stated in the preceding paragraph was found.

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THE TERMINAL ELECTROCARDIOGRAM: TWENTY-THREE CASE REPORTS AND A REVIEW OF THE LITERATURE

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THE mechanism of death in the human heart has been an interesting topic for many centuries. The ancients believed the left auricle to be the last portion to stop contracting visibly. In 1850, Hoffa and Ludwig[18] showed that electrical stimulation of the mammalian heart caused ventricular fibrillation and death. In 1887, MacWilliam[26] predicted ventricular fibrillation to be the principal factor in sudden death. In 1912, Robinson[33] reported the first electrocardiograms taken in the agonal state. In 1915, Allbutt[1] proposed an overwhelming, sudden vagus stimulation with complete standstill as a cause of sudden death. Since then, many authorities[4,15,17,21,41] have come to believe that ventricular fibrillation probably is the main factor in sudden death of patients with severe heart disease with angina pectoris and/or myocardial infarcts. However, Grieco and Schwartz[10] have predicted recently that as many sudden deaths in coronary heart disease are caused by standstill as by sudden ventricular fibrillation. There has been a great deal of discussion as to the possible patterns in terminal electrocardiograms.

We are presenting twenty-three cases in which the electrocardiograms were obtained before and during the terminal activity of the heart. The available literature has been reviewed and will be discussed briefly in connection with our findings and the experimental data of Harris[15b] on the electrocardiograms of dogs dying from anoxemia, from hemorrhage, and from clamping of a coronary artery.

METHOD

When practical, the electrodes were attached to the moribund patient before clinical death. The three standard leads were obtained and also a few chest leads. Tracings were taken intermittently or continuously on Lead *II* until the string became motionless. Several cases were obtained during operations under general anesthesia. In two cases, hearts that were "dead" clinically by electrocardiogram were revived. Both patients died some time afterward, but the original death was used without obtaining records of the "second" death. Unless otherwise stated, clinical death occurred some time before the electrocardiographic tracing became flat.

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CASE REPORTS

CASE 1.—R. W., a woman, 40 years of age. *Hypertensive cardiovascular disease with recent hemorrhage into the pons.* The patient collapsed suddenly on the street and was admitted in coma with left-sided paralysis. Bloody spinal fluid was noted. She died in one hour. Necropsy revealed recent hemorrhage into the pons with extension. The heart, weighing 490 grams, was dilated and hypertrophied. The kidneys revealed chronic pyelitis and moderate nephrosclerosis.

Electrocardiogram: Initial tracing revealed a ventricular rhythm at a rate of 115 per minute with occasional ectopic ventricular beats. Rate suddenly slowed to 59 per minute with increasing intraventricular block. The ventricles stopped suddenly while the auricles continued to beat for about thirty seconds at a rate of 45 per minute.

CASE 2.—A. F., a man, 42 years of age. *Carbon tetrachloride poisoning with uremia.* The patient was admitted with symptoms of renal failure and died on the twenty-first hospital day despite peritoneal lavage. Necropsy revealed severe acute nephrosis, necrosis of the liver, diffuse bronchopneumonia of both lungs, and a dilated heart weighing 470 grams.

Electrocardiogram: Initial tracings during hospitalization revealed right bundle branch block that disappeared temporarily during peritoneal lavage (potassium intoxication ?). At death, regular sinus rhythm was followed by increasing P-R interval. Nodal rhythm supervened. Finally, a slow ventricular rhythm appeared abruptly. This merged into flutter and terminal ventricular fibrillation.

CASE 3.—P. S., a woman, 59 years of age. *Severe diabetes with recent myocardial infarction.* This patient was admitted because of a history suggestive of myocardial infarction three weeks previously and progressive dyspnea. She died suddenly on the fourteenth hospital day while in uremia. Necropsy was not performed.

Electrocardiogram: On admission, tracing revealed evidence of acute anterior infarction. Digitalization slowed the rate to 40 per minute. Wandering pacemaker was then noted. The terminal electrocardiogram revealed a gradually widening QRS. There ensued periods of prolonged cardiac standstill interrupted by bizarre ventricular complexes. This continued for about fifteen minutes until complete standstill. No P waves were seen.

CASE 4.—C. C., a woman, 37 years of age. *Hypertension, central nervous system syphilis, sicklemia, and tuberculous keratitis.* Terminal hospitalization was for weakness and nausea. Flaccid paralysis of the lower extremities and nuchal rigidity were noted. Laboratory tests revealed the nephrotic syndrome. The spinal fluid Wassermann was positive. Death occurred on the tenth day. Necropsy revealed syphilitic meningoencephalitis and myelitis; hypertrophied and dilated heart (350 grams); stellate wrinkling and retraction of the aorta; sicklemia; and bilateral pyelonephritis.

Electrocardiogram: The record showed nodal tachycardia with ectopic ventricular beats until respirations ceased. Then the ventricular rate slowed and runs of several monophasic waves interrupted by long periods of standstill appeared. Caffeine and intracardiac adrenalin did not prevent complete standstill in four minutes.

CASE 5.—C. K., a man, 74 years of age. *Prostatic carcinoma with metastases.* A transurethral resection for urinary retention was done four months prior to the terminal admission because of anasarca. Total blood proteins were 3.9 Gm. per 100 cubic centimeters. Chest x-ray revealed fluid at both bases and possible metastases. The heart size was normal, but the liver was palpable three fingerbreadths below the costal margin. He died rapidly. Necropsy was not performed.

Electrocardiogram: Previous records showed left axis deviation and sinus coupling. Terminal strips revealed a slow ventricular rate without visible P waves. These waves were bizarre and were gradually reduced in amplitude. After two minutes there was no further movement of the string.

CASE 6.—L. H., a man, 60 years of age. *Diabetes mellitus, lymphatic leucemia, hemachromatosis, and tuberculous pneumonia.* The patient was hospitalized terminally and died suddenly

on the thirty-sixth day. Necropsy revealed the additional findings of arterial nephrosclerosis, marked sclerosis of the coronary arteries, and slight myocardial fibrosis.

Electrocardiogram (Fig. 1): Previous tracings revealed sinus tachycardia with low voltage in all leads. The terminal tracing was started when respirations were two per minute and the patient pulseless. It lasted five minutes, thirty-four seconds. Sinus tachycardia with low amplitude merged into slow nodal rhythm. Standstill then occurred and was followed by slow ventricular rhythm. This was followed by ventricular flutter and terminated in coarse fibrillation.

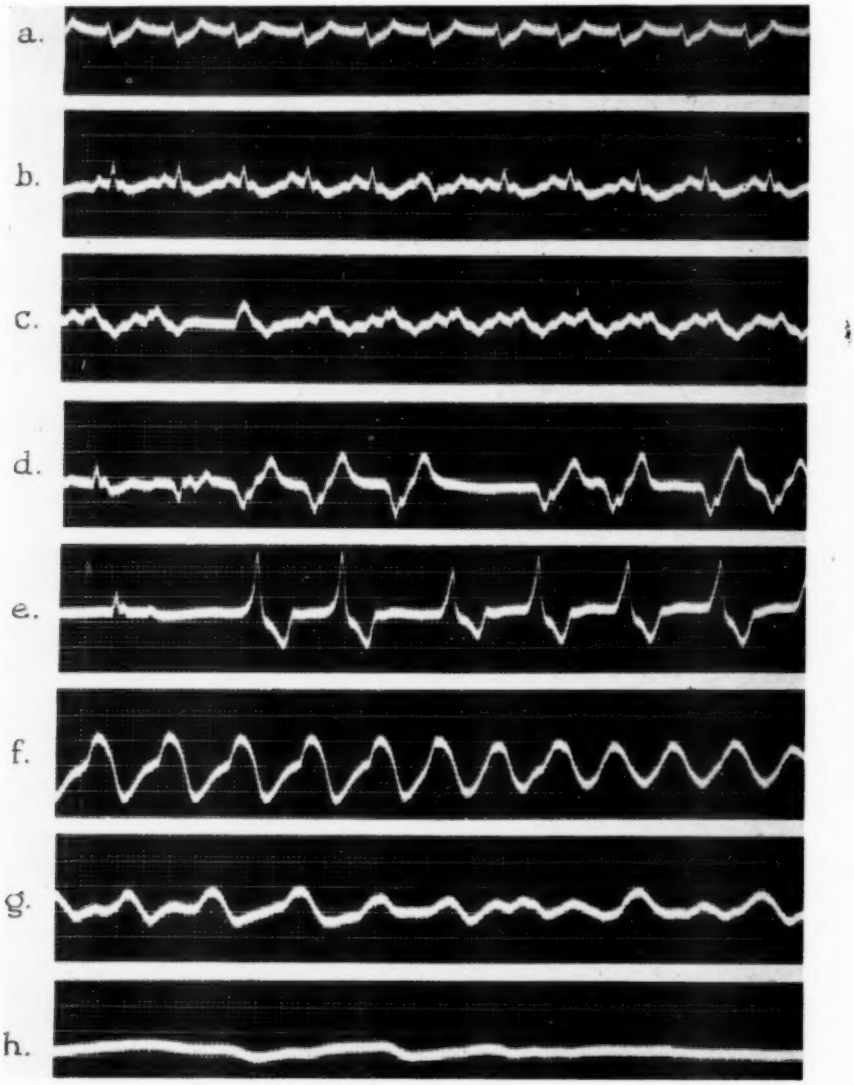

Fig. 1.—Case 6. See text for description.

CASE 7.—K. H., a woman, 55 years of age. *Diabetes mellitus, hypertension, arteriosclerotic heart disease, and recent and old myocardial infarcts.* The terminal hospitalization was due to severe angina pectoris. She was in shock and in congestive failure. She expired as the electro-

cardiographic tracing was started. Necropsy revealed marked stenosing coronary arteriosclerosis with recent and remote infarcts of the left ventricle. Diffuse arteriolar hyaline necrosis was found in the pancreas, kidneys, and adrenals.

Electrocardiogram (Fig. 2): The terminal record revealed prolonged P-R interval with intraventricular block, auricular standstill with slow ventricular rate, and final standstill.

CASE 8.—W. R., a man, 60 years of age. *Diverticulitis of the colon, peritonitis, and left hemiplegia.* On hospitalization, symptoms and signs suggested diverticulitis. X-ray confirmation was obtained. On the nineteenth day the patient developed peritonitis. On the next day, left hemiplegia occurred and he died suddenly while an electrocardiogram was being taken. Necropsy was not obtained.

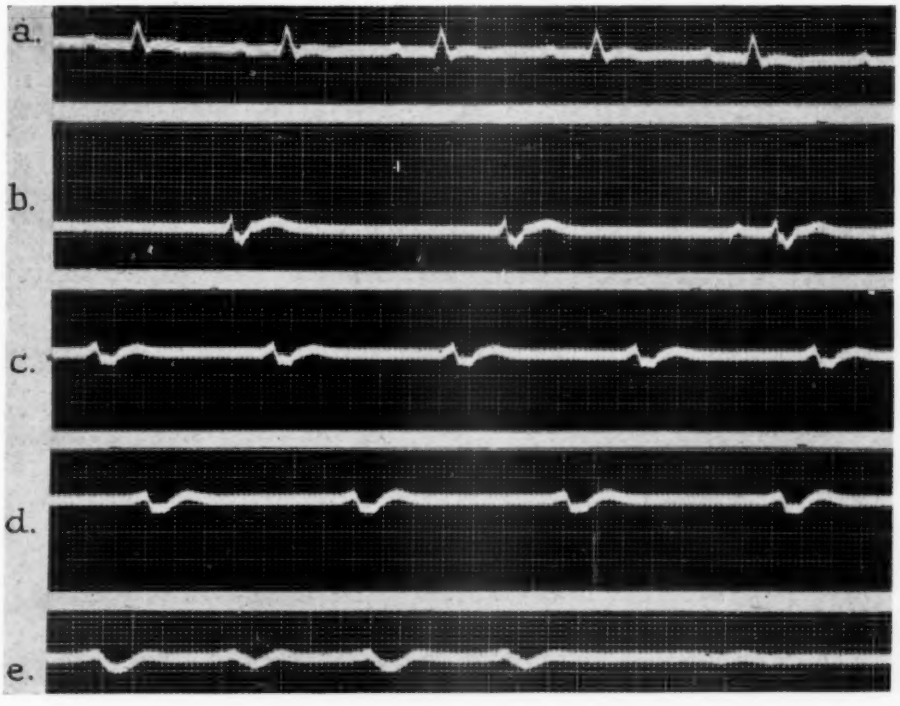

Fig. 2.—Case 7. See text for description.

Electrocardiogram: The standard leads showed sinus tachycardia and right bundle branch block. As he expired, the terminal strip revealed irregular ventricular complexes at a rate of 40 per minute with markedly elevated S-T segments. No P waves were noted. Short runs of ventricular tachycardia arising from varying foci were followed by gradual slowing and widening of the beats. Finally, periods of complete standstill alternating with short runs of bizarre ventricular complexes ended in standstill.

CASE 9.—M. K., a man, 62 years of age. *Hypertensive and arteriosclerotic heart disease with recent and old myocardial infarcts.* This patient was hospitalized for suspected acute myocardial infarction. He was in congestive heart failure. The next morning, although seemingly comfortable, he died suddenly while a tracing was being taken. Necropsy revealed marked arteriosclerosis of the left coronary artery with a recent thrombus in the anterior descending branch. Other findings were remote infarcts of the posterior portions of the left ventricle and interventricular septum, splenic infarct, and recent and remote infarcts of the right auricular appendage.

Electrocardiogram (Fig. 3): Previous records revealed auricular fibrillation with digitalis effect, and just prior to admission, sinus arrhythmia with frequent auricular and ventricular ectopic beats. The agonal strip, which was run almost continuously for forty minutes, revealed coarse ventricular fibrillation followed by auricular flutter, standstill, and a few terminal, slow, monophasic ventricular (?) complexes.

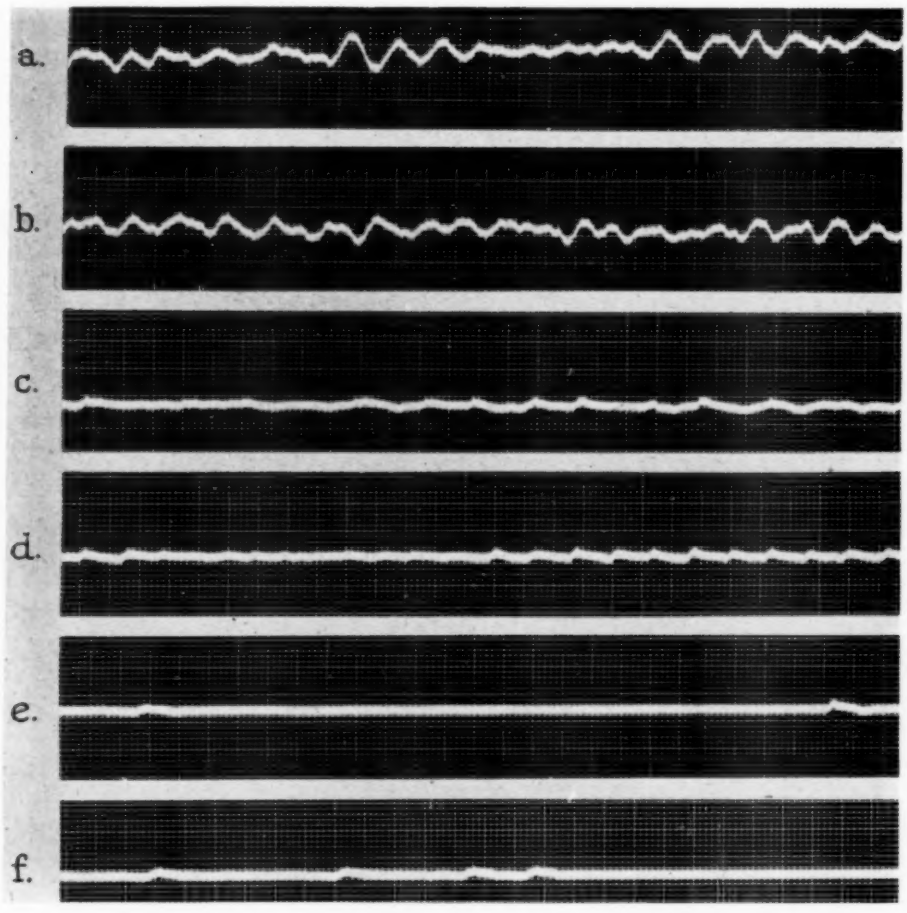

Fig. 3.—Case 9. See text for description.

CASE 10.—E. J., a boy, 10 years of age. *Comminuted fracture of right tibia with hemarthrosis and foreign body of the right knee joint.* During operation under gas-oxygen-ether anesthesia the pulse disappeared. The fibrillating ventricles were exposed and 5.0 c.c. of 5 per cent procaine were injected into the cavity of the right ventricle and the ventricles were shocked to standstill by the Wiggers technique.[42] The heart was massaged manually. After approximately twenty minutes, effective rhythm was obtained. The heart continued to beat for seventy minutes. Necropsy revealed moderate stenosis of the right coronary artery in addition to the expected findings.

Electrocardiogram: Tracings were taken after defibrillation. They first revealed auricular fibrillation with a ventricular rate of 45 per minute, low QRS complexes and depressed S-T segments. Twenty minutes later, auricular flutter at a rate of 66 per minute with a ventricular rate

of 17 per minute was followed by auricular standstill. After the onset of the terminal rhythm, ventricular fibrillation occurred.

CASE 11.—G. C., a man, 60 years of age. *Acute myocardial infarct.* While dancing, this man was stricken with an attack of substernal oppression. He gave a history of previous anginal attacks. While one of us was taking an electrocardiogram he collapsed suddenly and died. Necropsy was not permitted.

Electrocardiogram (Fig. 4): The three standard leads revealed normal sinus rhythm at a rate of 84 per minute with rare premature ventricular beats and the typical pattern of acute posterior myocardial infarct. During shifting to the chest lead, the patient collapsed and a record started a few seconds later revealed coarse ventricular fibrillation.

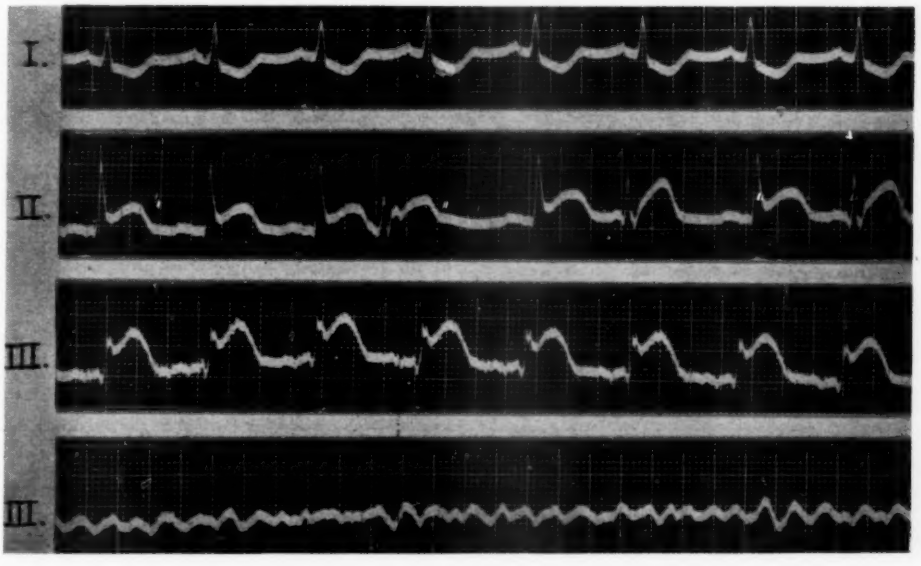

Fig. 4.—Case 11. See text for description.

CASE 12. H. G., a man, 68 years of age. *Hypertensive and arteriosclerotic heart disease.* This patient had been followed for many years and had suffered several attacks of congestive heart failure and a cerebrovascular accident. On admission he was confused and in acute congestive failure. Blood urea nitrogen was markedly elevated. Despite 1.0 mg. of Cedilanid given intravenously in divided doses, he died in eleven hours. Necropsy revealed pneumonia of both lower lobes, moderate stenosis of the aortic valve, marked generalized arteriosclerosis including the coronary and pulmonary arteries, acute fibrinous pericarditis, myocardial fibrosis, and left ventricular hypertrophy and dilatation (heart weighed 510 grams).

Electrocardiogram: The initial record revealed auricular fibrillation with a ventricular rate of 148 per minute. Following Cedilanid, nodal rhythm was noted at a rate of 70 per minute. The ventricular complexes broadened and the rhythm became irregular. The T wave, previously flat, became upright and many ectopic ventricular beats appeared. Finally, there was a sudden burst of ventricular fibrillation, with gradual decrease in amplitude, and standstill.

CASE 13.—C. G., a man, 71 years of age. *Hypertensive and arteriosclerotic heart disease; Stokes-Adams syndrome and congestive failure.* This patient was admitted for the last time in congestive failure. Despite digitalis, diuretics, and paracenteses, he died suddenly on the fourteenth hospital day after a series of attacks of cardiac standstill lasting from fifteen to forty-five seconds. Necropsy was not permitted.

Electrocardiogram: The terminal tracing showed slightly irregular, upright, monophasic QRS complexes at a rate of 84 per minute with no visible P waves. These ventricular complexes suddenly stopped, revealing notched P waves at a rate of 35 per minute. Ventricular rhythm again started after twenty seconds at the rate of 75 per minute. This lasted about ten seconds, and the terminal event was gradual slowing and flattening of the auricular waves at a rate of 22 per minute with complete ventricular standstill.

CASE 14.—M. L., a woman, 27 years of age. *Patent ductus arteriosus with subacute bacterial endocarditis due to hemolytic Staphylococcus albus.* The patient was admitted with a typical history, signs, and symptoms of both conditions. After preliminary penicillin therapy, ligation of the duct was attempted under gas-oxygen-ether anesthesia. As the pericardium was opened, the arterial pressure dropped suddenly. A generalized convulsion started on the left side, and soon after, the heart stopped. After massage, local procaine, and defibrillation, ventricular fibrillation persisted. After about six more shocks, fairly normal contractions started. After the intracardiac injection of adrenalin, the heart beat for five minutes and again stopped. Massage was successful and the ductus was ligated with disappearance of the thrill. The chest was closed and the patient began to breathe spontaneously. She died nine hours later without regaining consciousness. Necropsy revealed a ligated patent ductus arteriosus, subacute bacterial endocarditis of the pulmonary valve, recent pulmonary infarcts of the lower lobes, and what appeared to be an ante-mortem embolus in a cerebral artery on the right.

Electrocardiogram: Tracings were taken from 8:25 A.M., just before anesthesia, until the patient left the operating room. The last nine hours were not recorded. The first strip showed sinus tachycardia. This continued until just before the convulsion when ectopic ventricular beats occurred. Next there were short bursts of supraventricular beats until complete standstill occurred. This was followed by coupled ventricular beats. Then ventricular flutter merged into ventricular fibrillation. With further shock therapy the tracings reverted to ventricular tachycardia and eventually auricular fibrillation with fast ventricular rate.

CASE 15.—I. F., a man, 52 years of age. *Arteriosclerotic heart disease with remote myocardial infarction and fibrous obliteration of pericardium.* This man was admitted for pericardiectomy because of calcification of the pericardium overlying the right ventricle. He had suffered a myocardial infarct nine years previously. Recently congestive failure had occurred. Under gas-oxygen-ether anesthesia, the heart stopped beating before the mediastinum was entered. Incision of the pericardium and cardiac massage produced a feeble beat. The wound was closed and the patient died several hours later. Necropsy revealed fibrous obliteration of the pericardium over the right ventricle; coronary arteriosclerosis with remote occlusions of the circumflex and anterior descending branches of the left coronary artery, remote calcified infarct and aneurysm of the anterior half of the left ventricle and interventricular septum, and the results of the recent surgery.

Electrocardiogram: Routine tracings before operation were typical of remote anterior infarction. During operation, sinus tachycardia was supplanted by ventricular standstill. This was followed by A-V dissociation with a slow, irregular ventricular rhythm of 35 per minute, while the auricular rate was 60 per minute. About an hour later, bizarre ventricular complexes with periods of standstill occurred. Next was noted ventricular standstill followed by slow, undulating ventricular waves (50 per minute). Then irregular ventricular complexes with retrograde P waves were noted and periods of complete standstill. Finally, a few rare waves, probably of auricular origin, terminated electrical activity.

CASE 16.—M. T., a woman, 49 years of age. *Hypertensive cardiovascular disease, dissecting aortic aneurysm, and syphilis.* About an hour before admission, the patient suffered excruciating back pain and vomited. On admission, as in the past, she was in congestive heart failure. She was given morphine sulfate and died suddenly while an electrocardiogram was being taken. Necropsy was not permitted.

Electrocardiogram: Previous records revealed left axis deviation and digitalis effect. On the first of the terminal records, standard leads revealed sinus tachycardia. The final strip showed A-V dissociation with the auricles beating at a rate of 60 per minute and the ventricles at 51 per

minute. The ventricular complexes were very wide and bizarre. The ventricular rate slowed to 12 per minute and stopped. P waves disappeared when the ventricular rate was 24 per minute.

CASE 17.—V. S., a woman, 30 years of age. *Air embolism.* This healthy woman was given a Rubin test for tubal patency under nitrous oxide anesthesia. At the end of the procedure, the blood pressure was unobtainable and respirations fell to 4 per minute. Within six to ten minutes the pericardium was incised and the heart beat restored after defibrillation and massage. There was evidence of air in the veins at this time. Later the chest was reopened and a hemorrhage stopped. Patient expired nine hours later. Necropsy revealed nothing beyond the expected surgical trauma and slight salpingitis.

Electrocardiogram: Tracings were started just after the emergency operation began. The first strip revealed right bundle branch block at a rate of 150 per minute. Next ventricular fibrillation alternated with flutter at 152 per minute. (During these strips the patient was dead clinically.) The next strip showed small ventricular complexes at a rate of 75 per minute which slowed to 20 to 30 per minute, with auricular fibrillation. Next the patterns of ventricular flutter, slow ventricular rhythm, ventricular fibrillation, ventricular flutter, and a multifocal ventricular rhythm occurred in that order. Finally, ventricular tachycardia at a rate of 136 per minute changed to sinus bradycardia at 46 per minute, and the last strip revealed a sinus tachycardia at 125 per minute. Records were not taken at the second "clinical" death.

CASE 18.—M. S., a woman, 62 years of age. *Massive, confluent bronchopneumonia with congestive heart failure.* This delirious patient was admitted with pneumonia of three weeks' duration. The liver was enlarged and ankle edema was noted. She died in a few hours. Necropsy revealed massive, confluent bronchopneumonia throughout both lungs. The heart appeared normal. The liver was congested.

Electrocardiogram: Supraventricular tachycardia with frequent ventricular premature beats changed to auricular fibrillation with a ventricular rate of 88 per minute. Then broad ventricular complexes occurred at 54 per minute. Finally, ventricular tachycardia appeared (rate 163 per minute) and sudden complete standstill terminated the record.

CASE 19.—A. G., a man, 65 years of age. *Hypertension, gastrointestinal bleeding, and (?) acute myocardial infarction.* Prior to admission, this patient had substernal oppression on exertion. On admission, he stated that hematemesis and melena had been present for three days. The hemoglobin dropped during hospital stay from 9.5 Gm. to 8.0 Gm. per 100 cubic centimeters. On the third hospital day, a crushing substernal pain occurred with shock. He died in forty-five minutes while an electrocardiogram was being taken. Necropsy was refused.

Electrocardiogram: Previous records taken on his first two hospital days revealed abnormal left axis deviation. The terminal strip showed coarse ventricular fibrillation.

CASE 20.—A. W., a man, 39 years of age. *Hypertensive heart disease with recent and old myocardial infarcts.* The patient gave a history of myocardial infarct six months prior to admission and stated he "shot several pulmonary emboli." Fifteen minutes before admission he noted crushing substernal oppression. Despite medication, his symptoms increased and he expired less than an hour after admission while an electrocardiogram was being taken. Necropsy was refused.

Electrocardiogram: The initial standard and chest leads revealed sinus tachycardia with intraventricular conduction defect. This changed to nodal rhythm with dropped ventricular beats (rate 22 per minute). This changed to A-V dissociation (auricular rate 50 and ventricular rate 33 per minute). Finally, after a brief period of nodal rhythm (rate 28 per minute), the P waves disappeared and there were bizarre ventricular complexes at a rate of 10 per minute. Cardiac standstill then terminated the record.

CASE 21.—A. C. S., a man, 75 years of age. *Benign prostatic hypertrophy and angina pectoris (?).* The patient was admitted because of urinary retention. He gave a history suggestive of anginal syndrome. Physical examination revealed no cardiovascular abnormalities except peripheral arteriosclerosis. The heart was within normal limits by x-ray examination. The first stage prostatectomy was uneventful. During the second stage, under open-drop-ether anesthesia, the

heart rate quickened and the blood pressure rose rapidly. Pulmonary edema ensued. Following intravenous administration of Cedilanid, 1.6 mg., and aminophylline, the patient expired within an hour. Necropsy was not obtained.

Electrocardiogram: The initial tracing upon admission showed bradycardia and left axis deviation. The terminal strip, started about fifteen minutes before clinical death, revealed sinus tachycardia (rate 188 per minute) which shifted suddenly to ventricular tachycardia (rate 172 per minute). Later ventricular fibrillation occurred. The next strip showed small fibrillatory waves for about two seconds. Standstill followed for another few seconds. Then there appeared some irregularly spaced, bizarre ventricular complexes at a rate of 5 to 10 per minute which lasted several minutes and were followed terminally by a fine ventricular fibrillation that lasted six seconds.

CASE 22.—W. H., a man, 50 years of age. *Hypertensive cardiovascular disease with recent and old infarcts of lungs and heart.* He had been digitalized for congestive heart failure but had taken no digitalis in the month prior to hospitalization. He was admitted with hemoptysis. He received 1.4 Gm. of digitalis by vein and muscle in the eighteen hours prior to death. While an electrocardiogram was being taken, he died suddenly. Necropsy findings consisted of a dilated heart weighing 940 grams with recent infarction of the right auricle, old healed infarction of the apex of the left ventricle and interventricular septum, and old and recent infarcts of the lungs. There was marked, generalized, severe arterial and arteriolar sclerosis.

Electrocardiogram: Previous tracing revealed left bundle branch block. Terminal strip revealed supraventricular tachycardia (rate 150 per minute) with prolonged QRS and terminal ventricular fibrillation.

CASE 23.—J. M., a man, 87 years of age. *Arteriosclerotic heart disease with Stokes-Adams syndrome and aortic stenosis.* (The record of this patient was taken by Dr. Austin Weisberger who kindly gave us permission to include it in this study.) This aged man was admitted to a Naval Hospital because of frequent bouts of fainting. He was not in congestive failure. Treatment with ephedrine sulfate was ineffective. His terminal attack ended in anoxemic convulsions. The heart continued beating at least two hours after respirations ceased. At necropsy the findings were marked, generalized arteriosclerosis, stenosis of the aortic valve, and a hypertrophied heart.

Electrocardiogram: Tracing taken two months prior showed sinus bradycardia with a rate of 56 per minute. Tracing about one week prior to death revealed ventricular standstill upon carotid sinus pressure. The record several days prior to death showed dissociation with an auricular rate of 62 and a ventricular rate of 32 per minute. The terminal tracing started with frequent episodes of ventricular asystole. Bizarre ventricular complexes ensued at a slow rate. The rate increased to 120 per minute and then slowed. In the meantime, the auricles beat independently at about 70 per minute. Finally, there was sudden complete ventricular asystole. The auricular rate slowed to 30 per minute and stopped for five seconds. This was succeeded by irregular, wide, ventricular waves at a rate of 70 per minute with inverted T waves. Then, regular small ventricular complexes with deep Q and upright T waves occurred. Then followed ventricular flutter at a rate of 70 per minute lasting twenty seconds. These waves became irregular, smaller, and ceased gradually.

SUMMARY OF OUR CASES

Our twenty-three patients ranged in age from 10 to 87 years. No definite heart disease could be found in seven cases (Table I). Of these latter patients, in one case, sudden death was due to ventricular fibrillation, while in three, ventricular fibrillation was but the terminal phase occurring long after "clinical" death. The remaining three patients of this group showed no ventricular fibrillation. The heart slowed and then stopped abruptly. Of the sixteen cases of obvious heart disease, seven ended with ventricular fibrillation (Table II). Of

TABLE I. DEATHS NOT DUE TO HEART DISEASE

PATIENT	SEX	AGE	NECROPSY	DIAGNOSIS	TERMINAL ECG PATTERNS
2. A. F.	♂	42	Yes	Carbon tetrachloride poisoning, uremia	Ventricular slowing and fibrillation
5. C. K.	♂	74	No	Transurethral resection	Ventricular slowing and standstill
6. L. H.	♂	60	Yes	Leucemia, tuberculosis	Ventricular slowing and fibrillation
8. W. R.	♂	60	No	Peritonitis, hemiplegia	Ventricular slowing and fibrillation
10. E. J.	♂	10	No	Fractured left tibia, foreign body	Ventricular fibrillation (sudden)
17. V. S.	♀	30	Yes	Air embolism	Ventricular fibrillation and flutter
18. M. S.	♀	65	Yes	Massive bronchopneumonia	Ventricular tachycardia and sudden standstill

Summary: Seven cases, four ventricular fibrillation

TABLE II. DEATHS DUE TO HEART DISEASE

PATIENT	SEX	AGE	NECROPSY	DIAGNOSIS	TERMINAL ECG PATTERNS
1. R. W.	♀	40	Yes	Hypertension, cerebral hemorrhage	Ventricular slowing and standstill; auricles 30″ longer
3. P. S.	♀	59	No	Diabetes, myocardial infarct	Ventricular slowing and standstill
4. C. C.	♀	37	No	Hypertension, CNS syphilis, sicklemia	Ventricular slowing and standstill
7. K. H.	♀	55	Yes	Hypertension and arteriosclerosis, diabetes, old and recent infarct	Ventricular slowing and standstill
9. M. K.	♀	62	Yes	Hypertension and arteriosclerosis, recent and old infarct	Sudden ventricular fibrillation (standstill and slow ventricular rate)
11. G. C.	♂	60	No	Myocardial infarct	Sudden ventricular fibrillation
12. H. G.	♂	68	Yes	Pneumonia, hypertension and arteriosclerosis	Ventricular slowing and fibrillation
13. C. G.	♂	71	No	Hypertension and arteriosclerotic disease	Ventricular slowing and standstill; auricles continued for short time
14. M. L.	♀	27	Yes	Subacute bacterial endocarditis and patent ductus arteriosus	Ventricular slowing and standstill
15. I. F.	♂	52	Yes	Constrictive pericarditis, remote infarct	Ventricular slowing and standstill
16. M. T.	♀	49	No	Hypertensive cardiovascular disease,? Dissecting aneurysm	Ventricular slowing and standstill
19. A. G.	♂	65	No	Gastrointestinal bleeding. Acute infarct	Sudden ventricular fibrillation
20. A. W.	♂	39	No	Arteriosclerotic heart disease and recent infarct	Ventricular slowing and standstill
21. A. S.	♂	73	No	Prostatism, anginal history, op. death	Sudden ventricular fibrillation
22. W. H.	♂	50	Yes	Hypertension, cardiovascular disease, recent and old infarcts	Sudden ventricular fibrillation
23. J. M.	♂	87	Yes	Aortic stenosis, Stokes-Adams Syndrome	Ventricular slowing and fibrillation

Summary: Sixteen cases, seven ventricular fibrillation

the eight patients with recent or old myocardial infarction, four died suddenly as a result of the abrupt onset of ventricular fibrillation, while the other four patients died suddenly with slowing and abrupt standstill. Fifteen of the sixteen patients with diseased hearts died rapidly. In only five of these was death directly due to the onset of ventricular fibrillation.

DISCUSSION OF THE LITERATURE, EXPERIMENTAL WORK, AND OUR CASES

Sudden Death.—We have reviewed the literature, which is summarized briefly in Table III. Including our cases, eighty cases of heart disease were noted while seventy-six patients died of other causes. Thirty-one of the heart cases and twenty-six of the other cases terminated in ventricular fibrillation. On careful study of the cases, we found only eight in which sudden death was directly due to the onset of ventricular fibrillation. An equal number of deaths were

TABLE III. PREVIOUS REPORTS OF THE TERMINAL ELECTROCARDIOGRAM

	AUTHOR	YEAR	TOTAL CASES	HEART DISEASE	VENTRICULAR FIBRILLATION	OTHER DISEASES	VENTRICULAR FIBRILLATION
1	Robinson[32]	1912	7	0	0	7	1
2	Halsey[11]	1915	1	0	0	1	1
3	Dieuaide and Davidson[5]	1921	2	2	0	0	0
4	Schellong[34]	1923	6	3	0	3	2
5	Willius[43]	1924	4	2	2	2	1
6	Kahn and Goldstein[20]	1924	7	4	0	3	2
7	Reid[32]	1924	1	1	1	0	0
8	Martini and Sckell[28]	1928	17	8	2	9	0
9	Turner[38]	1931	4	4	0	0	0
10	Hamilton and Robertson[12]	1933	1	1	1	0	0
11	Meyer, P.[30]	1934	1	1	1	0	0
12	Calandre and Rodriques[3]	1934	1	1	1	0	0
13	Duvoir and Pollet[6]	1934	2	0	0	2	1
14	Herles[16]	1934	10	6	3	4	2
15	Laubrey and Degos[23]	1934	6	0	0	5	0
16	Buccianti[2]	1934	*				
17	Jezer, et al.[19]	1936	2	2	0	0	0
18	Vela[39]	1935	1	1	1	0	0
19	Misao, et al.[31]	1937	(30)	?	(9)	?	—
20	Sigler, et al.[35]	1937	20	10	3	10	4
21	Hanson, et al.[14]	1937	25	7	2	18	8
22	Grieco and Schwartz[10]	1938	1	1	0	0	0
23	Smith[36]	1939	1	1	1	0	0
24	Levin[24]	1939	2	0	0	2	0
25	Goodrich and Needles[9]	1940	2	2	1	0	0
26	Fritzche[8]	1940	1	0	0	1	0
27	Thompson[37]	1941	1	1	1	0	0
28	Franke[7]	1942	*				
29	Likoff, et al.[25]	1944	3	3	1	0	0
30	Krell[22]	1944	1	1	1	0	0
31	Marchand and Finch[27]	1944	2	0	0	2	0
32	Volini, et al.[40]	1945	2	2	2	0	0
33	Stroud and Feil	1947	23	16	7	7	4
	Totals		187	80+	40	76	26

*Paper not available.

due to standstill of the heart. In all these cases, the history or necropsy findings showed coronary heart disease.

Harris [15b] points out in his paper on acute experiments in dogs that occlusion of a coronary arterial branch for ten minutes will result in ventricular fibrillation in about 50 per cent of the cases, either initially or upon release of the occlusion. The cause of the ventricular fibrillation is due to rapid, repetitive ectopic systoles that shorten the period of refractoriness and/or slow conduction.[15a] It must be remembered that two important differences exist between our series and that of Harris. First, he is dealing with animals in which the coronary arteries and myocardium are presumably healthy before the experiment, while our cases of heart disease are obviously abnormal. Second, in dogs the induction of ventricular fibrillation results in permanent fibrillation unless defibrillation is performed.[42] In human subjects, ventricular fibrillation is not necessarily a permanent event, as there are a number of case reports in which spontaneous return to regular rhythm has been noted. In the literature we reviewed, although no recoveries occurred, a small number of the patients returned to orderly ventricular excitation after the burst of ventricular fibrillation.

Slow Death (Anoxic and Hemorrhagic Shock).—From our cases and those in the literature a fairly consistent pattern evolves. However, many exceptions prove the rule and no prediction can be made from the clinical findings in an individual case as to the terminal electrocardiographic patterns. The sequence of events is as follows: The initially rapid rate with sinus rhythm slows. Ectopic supraventricular beats may arise. There is prolongation of the auriculoventricular conduction time. Then excitation is initiated in the A-V node. Next, auricular activity ceases as the ventricular pacemaker develops. At this time, if many ectopic ventricular foci become active, ventricular flutter and fibrillation may ensue. Then, either the rate slows and the heart stops, or the rate increases and again a flutter-fibrillation may occur. In rare instances, auricular waves may be seen after all ventricular activity has ceased. The QRS widens and is reduced in amplitude. The T wave becomes larger and if inverted, becomes upright. Finally, the QRS and T merge into a monophasic, positive wave. The *x* wave of Shellong[34] can sometimes be seen between the QRS and T waves. It is usually upright. If auricular fibrillation was present previously, the rate slows and a regular nodal rhythm occurs. Auricular fibrillation rarely occurs. Dissociation of auricular and ventricular waves may occur. The most extreme example was cited by Fritzche[8] in which three different ventricular waves occurred independently. Two of them probably represented "partial systole" in which a small, localized area of ventricular muscle beat independently of the main muscle mass. In summary, then, the course of events is sinus slowing, nodal rhythm, ectopic ventricular systoles, ventricular rhythm, slowing, and stoppage. Ventricular fibrillation occurs usually when there is ventricular tachycardia and ectopic ventricular beats or following a period of asystole.

Harris[15b] has shown experimentally (in dogs) that the pattern we have described is seen in prolonged anoxemia or hemorrhage with the induction of shock. He has shown that sectioning of the vagus nerves will prevent the slow-

ing initially. He also showed that eventually the pattern will occur even with sectioning of the vagus nerves and suggests that it is then a *local* anoxic and metabolic reaction.

Therapeutically, in anoxemic emergencies where the individual is otherwise in good condition generally, the vagal implication suggests that the use of atropine may prevent cardiac standstill.

SUMMARY

1. Twenty-three cases in which terminal electrocardiograms were observed have been reviewed in conjunction with a review of the literature and experimental work.

2. The electrocardiographic pattern of anoxic and/or hemorrhagic shock and the role played by the vagus nerves were described.

3. The terminal electrocardiogram showed ventricular complexes which were usually aberrant in form and slow in rate. Permanent standstill occurred without ventricular fibrillation in 50 per cent of the cases.

4. We have reported eight sudden deaths associated with coronary heart disease and found an equal number in the literature. Of the sixteen deaths, eight were due to a sudden burst of ventricular fibrillation and eight to sudden ventricular standstill.

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THE CHANGING INTENSITY OF THE FIRST SOUND IN AURICULAR FLUTTER, AN AID TO THE DIAGNOSIS BY AUSCULTATION

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THE bedside diagnosis of auricular flutter is generally regarded as being difficult or impossible to make with any degree of accuracy. In most instances, its recognition first becomes apparent after electrocardiographic study. There are, however, some findings which lead one to suspect its presence, and with increased experience, even definite diagnoses can be made.

When the heart rate is rapid and regular (130 to 170) and carotid sinus stimulation produces some temporary slowing followed by an irregular and "jerky" retreat to the former regular rate, auricular flutter is likely to be present (Fig. 1). If the heart rate is slow and regular and the possibility of auricular flutter is kept in mind, a brief exercise test may reveal the true nature of the abnormality. The rate may suddenly double (that is, change from 70 to exactly 140), or it may become rapid and irregular. In both instances, the increased rate is likely to return to the previous slow regular rhythm in a few minutes on resting (Fig. 2). The test can be employed if the heart rate is already irregular, as it may become more rapid and perfectly regular on exercise (Fig. 3), whereas auricular fibrillation, with which it can be confused, will retain its irregular rhythm (Fig. 4). The effect of a deep inspiration may also prove valuable. Occasionally, this not only produces a slowing but causes the rhythm to become more irregular than is ordinarily observed in other conditions.

A further point that may be helpful in diagnosis is the actual rate of the tachycardia. If the rate is 190 to 200 and perfectly regular, it is extremely unlikely that flutter is present. The auricular rate would of necessity be either 190 to 200 with a 1:1 rhythm or 380 to 400 with a 2:1 block. The former possibility can be fairly well ruled out because 1:1 flutter is extremely rare and the auricular rate of 190 is too slow (if untreated). The latter is very unlikely because the auricular rate in flutter rarely exceeds 360 (except with thyrotoxicosis and during fever).

The purpose of this paper is to report our observations on a new sign which is commonly present in auricular flutter, that is, a changing intensity of the first sound. This phenomenon is similar to that observed in other conditions, and

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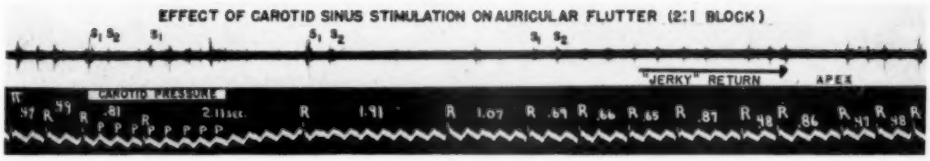


Fig. 1.—Carotid pressure produced prompt marked ventricular slowing, not affecting the flutter waves (*P*). Note "jerky" return to normal rhythm indicated by differences in R-R intervals. Patient was a 67-year-old man with paroxysmal auricular flutter.

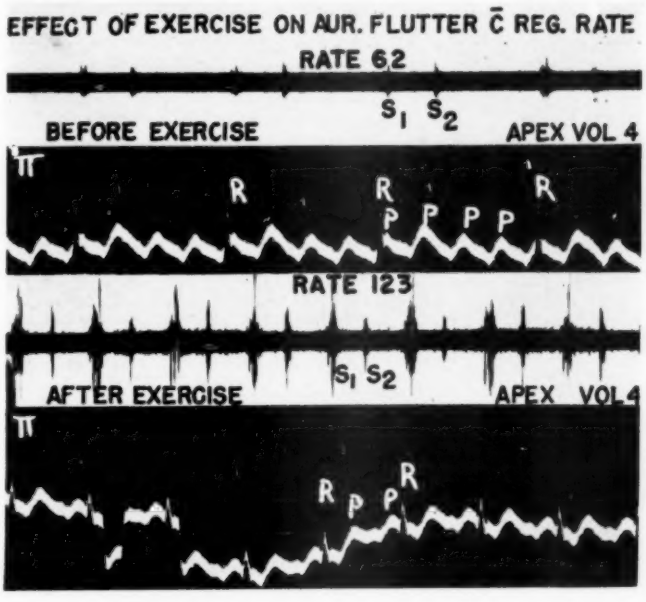


Fig. 2.—A 39-year-old man with paroxysmal auricular flutter. Note doubling of rate (62 to 123) after two minutes of exercise consisting of "hopping up and down." The mechanism changed from 4:1 block to 2:1 block.

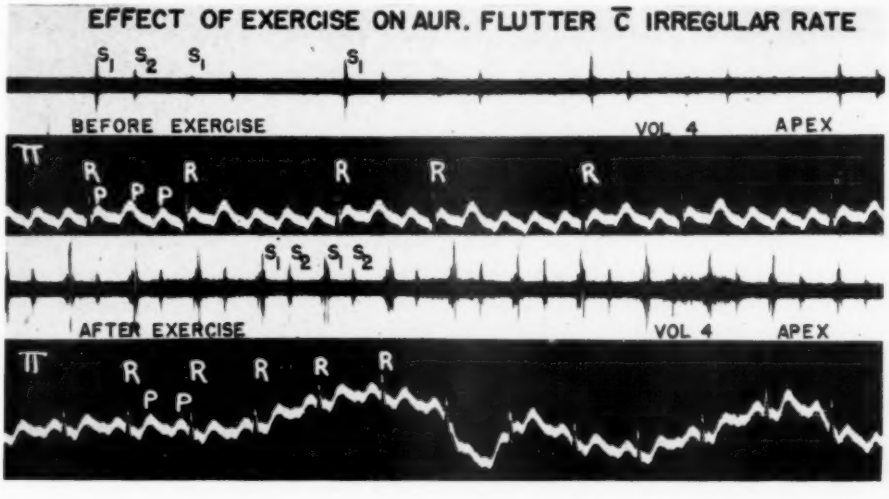


Fig. 3.—Note irregular rate (65) with flutter of varying block, 3:1, 5:1. Following exercise, the rate became regular (123) with a 2:1 block. A 39-year-old man with no organic heart disease.

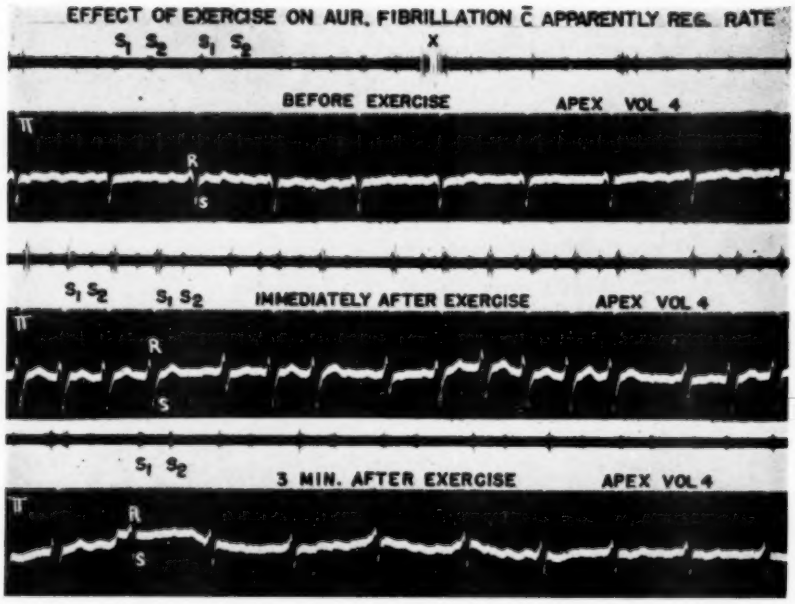


Fig. 4.—Upper tracing shows auricular fibrillation with only very slight irregularity. Heart sounds (S_1, S_2) constant. Artefact (X) due to breathing. Exercise brought out irregularity (middle tracing). Three minutes later (lower tracing) heart had returned to original rhythm. This 59-year-old man had hypertensive heart disease with failure.

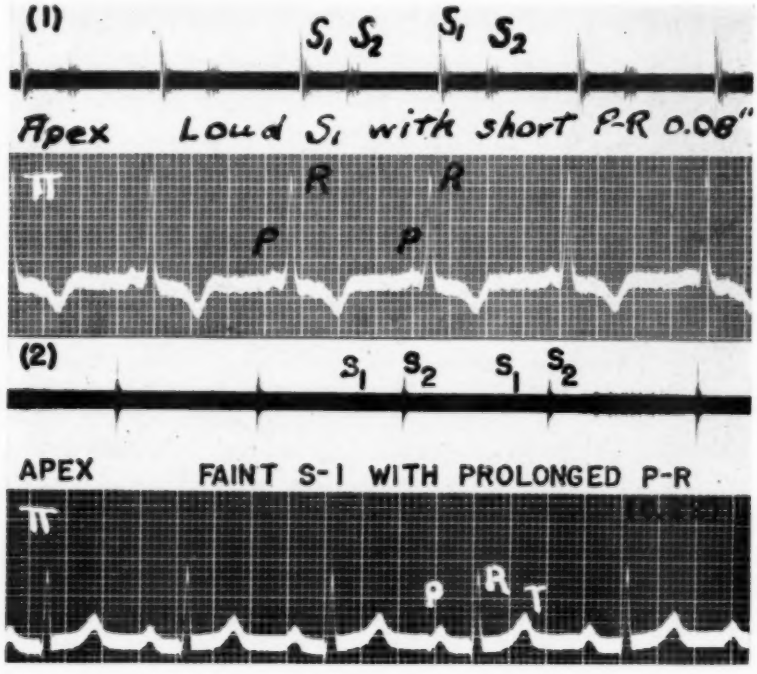


Fig. 5.—Upper tracing shows loud first sound (S_1) with short P-R interval (.08 second). Patient was a 24-year-old man with essential hypertension. Lower tracing shows almost inaudible first sound (S_1) with only slightly prolonged P-R (.22 second). Patient was a 24-year-old woman with Gaucher's disease.

the mechanism can probably best be appreciated by a brief review of the relationship of the P-R interval to the intensity of the first sound. Although this concept is not new,[1] it is apparently not generally known or has not been adequately stressed. When the P-R interval is prolonged, the first sound is usually diminished (Fig. 5). It is not necessary that the P-R be much prolonged, for even an interval of 0.21 second or 0.22 second will produce a faint first sound. This is a clinical means, and the only auscultatory finding that can lead to the suspicion of first degree heart block. Conversely, as one might suspect, when the P-R interval is short, the first sound is increased (Fig. 5).

The relationship of the P-R interval to the intensity of the first sound is well illustrated in Fig. 6. This patient with first degree heart block (P-R interval 0.28 second) had a faint first sound. Following intravenous injection of 1.0 mg. of atropine sulfate, the P-R interval was shortened to 0.18 second with a marked increase in intensity of the first sound, although the heart rate was unaltered. Complete heart block (Fig. 7) is another decisive illustration of this phenomenon, because in this condition the auricles and ventricles are beating independently with frequently changing P-R relationships. Again, it will be noted that when the P-R interval is short, the first sound is loud, whereas when it is lengthened, the first sound is diminished. When the P wave coincides exactly with the QRS complex, there may be no increase in the first sound. This changing intensity of the first sound in complete heart block, or the so-called "bruit de canon," is almost pathognomonic of this condition (an exception is shown in Fig. 9). This sign was first described by Strazhesko[2] in 1906, and later by Griffith[3] in 1912. Additional light is shed on the problem by the observation that auricular fibrillation with a regular, idioventricular rhythm, such as occurs with overdosage of digitalis, shows a constant first sound (Fig. 7). This is in distinct contrast to the changing sounds in complete heart block at the same rate, and is added proof of the influence of auricular contraction on the intensity of the succeeding first sound. Another example is that of ventricular tachycardia. Here, also, the auricles and ventricles may be contracting independently. The changing intensity of the first sound in a tachycardia which does not respond to carotid sinus stimulation, especially if the rate is slightly irregular,[4] leads one to make the correct diagnosis of ventricular tachycardia. In Fig. 8 the loud sounds are generally preceded by a short P-R interval, giving the complexes of the electrocardiogram coincident with the loud sound a configuration practically similar in each case. In fact, one can predict, without looking at the phonocardiogram, which complex will correspond to a loud first sound.

In this study we have noted that a changing intensity of the first sound is also common in auricular flutter. This observation was actually "stumbled upon" as a result of the examination of an 89-year-old man with carcinoma of the prostate. Auscultation of the heart revealed a slow, apparently regular rate of 42 per minute with a marked changing intensity of the first sound. Complete heart block was suspected, but carotid sinus stimulation produced an immediate and prompt slowing of the ventricular rate, which is unusual with complete block. The electrocardiogram revealed a regular 5:1 auricular flutter and the

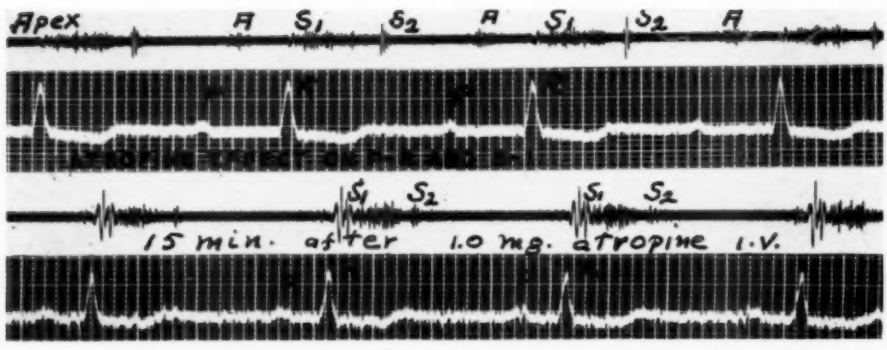


Fig. 6.—Upper tracing shows faint first sound (S_1) with long P-R interval (.28 second). Lower tracing shows loud first sound (S_1) fifteen minutes after 1 mg. atropine administered intravenously, when P-R interval was normal (.18 second). Auricular sounds (*A*) were detected in upper tracing.

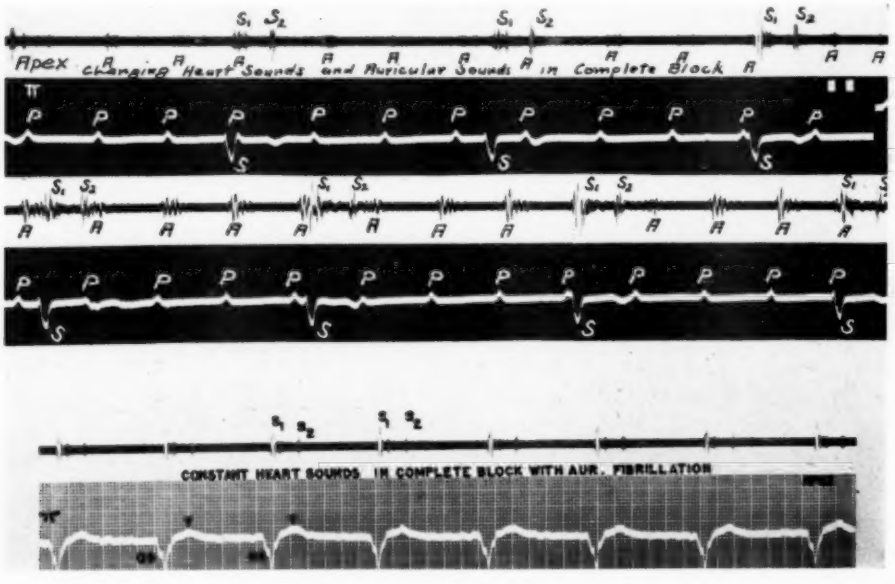

Apex changing Heart Sounds and Auricular Sounds in Complete Block
CONSTANT HEART SOUNDS IN COMPLETE BLOCK WITH AUR. FIBRILLATION

Fig. 7.—In upper tracing, note changing intensity of heart sounds, especially first sounds (S_1) in different cycles. Very loud are the sounds occurring with very short P-R intervals. When P and QRS occur simultaneously, first sound is not increased. Also note audible auricular sounds (*A*). Man, 75 years of age, had Adams-Stokes disease. In lower tracing, a case of complete block with auricular fibrillation shows no change in first sound. The auricles are not contracting and thus there is no P-R alteration.

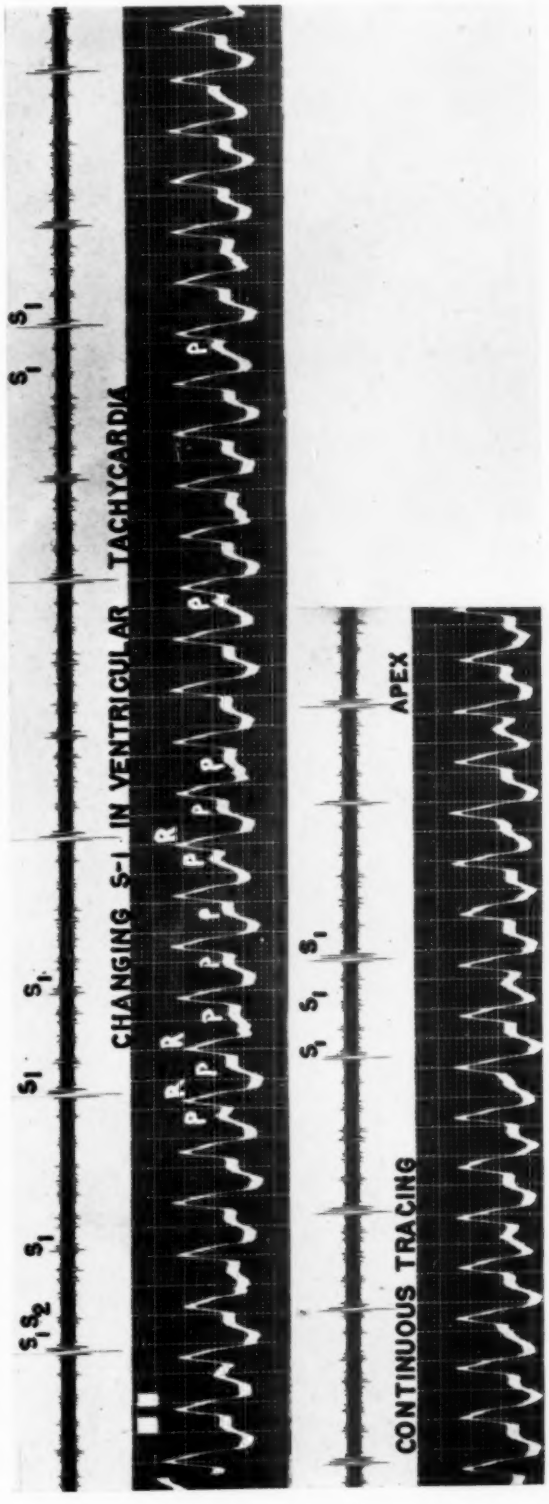


Fig. 8.—Note marked changing intensity of first sounds (S_1) with ventricular tachycardia. A changing P-R interval relationship is present. Each loud S_1 is generally preceded by ECG complexes almost identical in configuration. Patient was a 69-year-old man with Adams-Stokes disease.

phonocardiogram portrayed the changing intensity of the first sound noted clinically (Fig. 9). Careful measurement of the P-R intervals revealed that the ventricular response was not perfectly regular, but usually varied from 0.01 to 0.02 second in adjacent complexes. These minor differences, however, were sufficient to alter the over-all "P-R" relationship with the resultant change in the first sound. At other times, this patient was observed when his ventricular rate was noticeably irregular at the slow rate, and again, the first sound varied as before (Fig. 10).

In discussing the "P-R" relationship to the changing intensity of the first sound in auricular flutter, we purposely use quotation marks because of the obvious difficulty in deciding exactly where the "P" wave of auricular flutter begins. The differences of opinion as to whether the flutter wave begins with the upper peak, lowest point, or the "notch" on the down stroke has long been a controversial subject.[5,6] This remains unsettled, but we feel that the "notch" actually represents the beginning. However, for convenience and ease of measurement, we have arbitrarily chosen as the beginning of "P" the lowest point of the wave preceding the QRS complex. The tip of the R wave has been designated "R." In this way we have attempted to correlate a changing "P-R" relationship to the changing intensity of the first sound in auricular flutter, similar in principle to that observed in complete heart block and ventricular tachycardia. Proof that such a relationship actually exists is shown in Figs. 9 and 10. When the "P-R" was in the range of 0.10 to 0.20 second, the first sound was loud, the loudest sound being at a "P-R" relationship of around 0.14 to 0.15 second. Above and below this range, the sounds were characteristically diminished. It is evident from the tracings that very slight changes in the P-R interval can cause marked differences in the intensity of the first sound. Using this or another arbitrary "P-R" measurement, similar results were noted in the other cases, although the "range" for loud first sounds varied with the individual case.

This first experience served as a stimulus to search for similar findings in other cases of auricular flutter. Since then, ten patients with auricular flutter have been studied. Although the phonocardiograph was used to obtain objective proof, in these cases simple auscultation with an ordinary stethoscope revealed the significant changes. The changing intensity of the first sound has been noted in all but two instances.* These two exceptions were not surprising, as it could be predicted that whenever the "P-R" interval remained constant the first sound would not change in intensity. Such events are known to occur when there is a pure and constant 2:1 or 4:1 A-V block in auricular flutter. This is well illustrated in Fig. 11. Examination of the phonocardiograms of flutter with constant sounds revealed that the "P-R" relationship also remained constant. Only when there was a difference in the ventricular response, even though slight, was there a change in the first sound (except for the minor changes produced by respiration).

*A third case (middle tracing of Fig. 11) showed constant sounds when in pure 4:1 block and changing sounds at other times (third strip in Fig. 13).

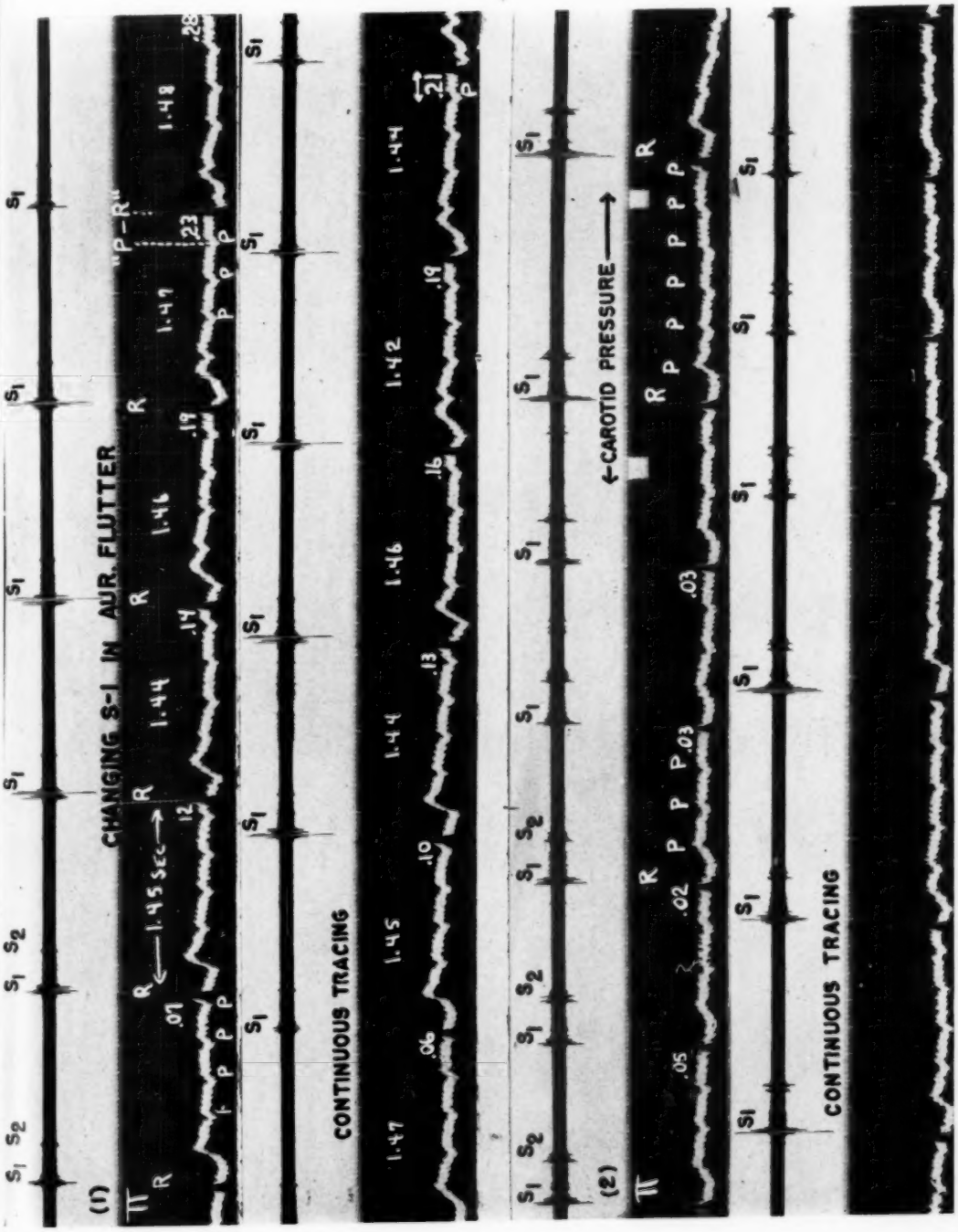
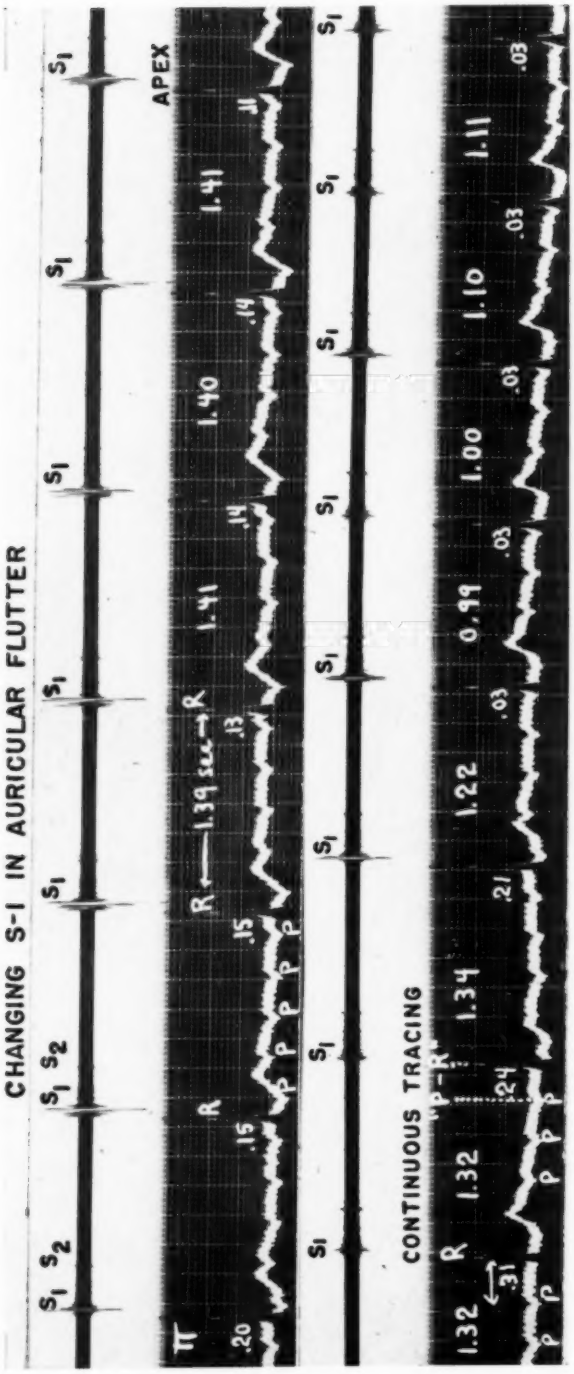


Fig. 9.—S_1 and S_2 are the first and second heart sounds. *P*, auricular flutter waves. R-R intervals and "*P-R*" intervals indicated in sounds. Note slight irregularity of ventricles and marked changing intensity of S_1. Loud first sounds generally occur in "*P-R*" range of .10 to .20 second. Lower two strips show ventricular slowing on carotid stimulation.


CHANGING S-I IN AURICULAR FLUTTER
APEX
CONTINUOUS TRACING
S1 S2
S1 S2
S1
S1
S1
S1
S1
S1
S1
S1
S1
S1
S1
S1
S1
S1
R
R
R
R
P
P
P

When there was a varying response in flutter such as 3:1, 2:1, and so forth, the first sound usually varied markedly, as would be expected. The loud sound, however, was not the result of a preceding longer diastole as is often noted in auricular fibrillation or following extrasystoles. The "P-R" relationship was

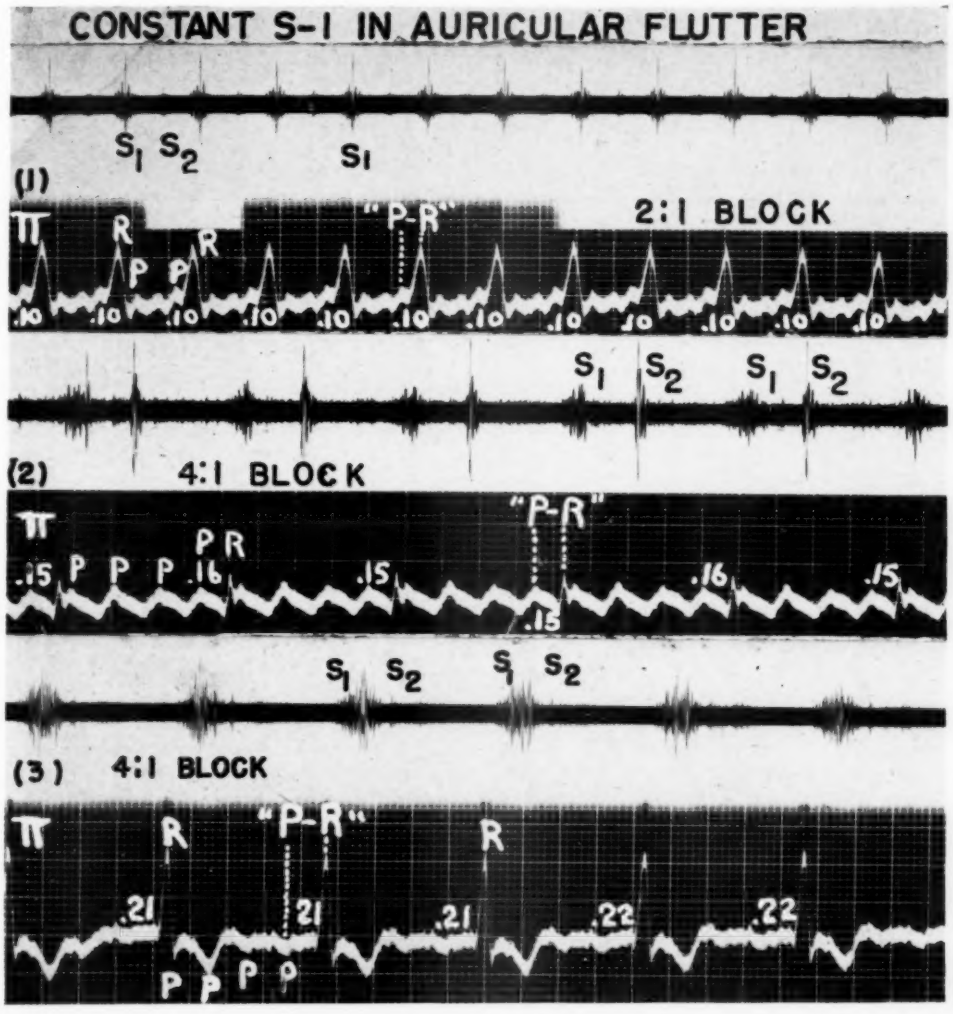


Fig. 11. — Three cases showing constant first sounds. The "*P-R*" interval in all cases remains practically constant. Note that *P* in the first and second case is arbitrarily measured from the peak of the flutter wave.

again the major factor as may be seen in Fig. 12. Here the loudest first sounds were those in a limited "P-R" range (in this case, about 0.19 to 0.24 second). When the first sounds did not fall in this "range" they were faint, even though the preceding diastole might have been prolonged.

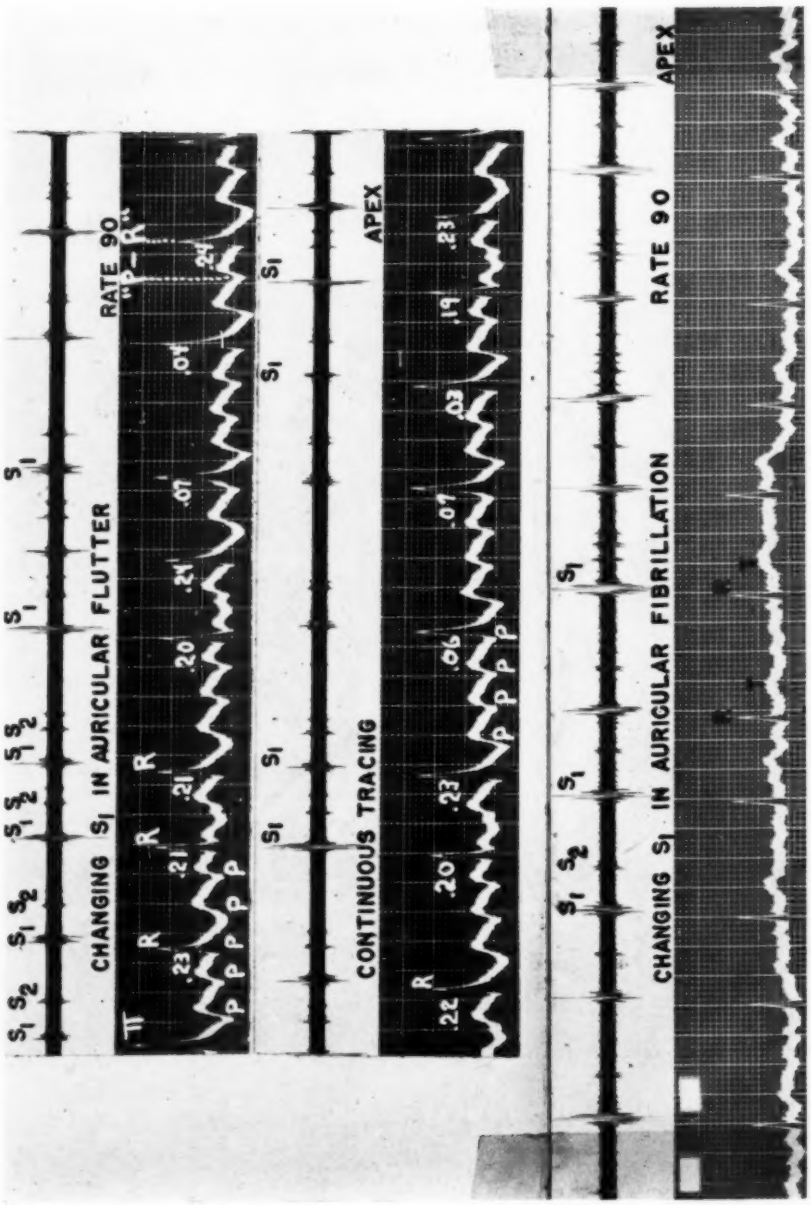


Fig. 12.—Note changing first sound (S_1) in upper tracing. Loud S_1 occurs in "*P-R*" range of .19 to .24 second with loudest at .20 second. Note faint S_1 with fourth and fifth complexes (second strip) which follow longer diastoles; seventh complex shows loud sound with short diastole. Lower tracing shows auricular fibrillation at same rate as above tracing with auricular flutter. The first sounds (S_1) are more constant with auricular fibrillation.

These observations help to explain the differences in the changes in intensity of heart sounds in auricular flutter and fibrillation. In the former, the auricles are actually contracting, whereas in the latter they are not. In fibrillation, therefore, the first sound should not vary in intensity as much from beat to beat, as the loudness of any heart sound would only depend on the length of the preceding pause and on the slight effect of respiration. In flutter there is the additional factor of auricular systole that has a much greater effect on the first sound. Fig. 12 shows a tracing of auricular flutter and one of fibrillation with the same ventricular rate. The changes in intensity of the first sound in the former are much greater than in the latter. Although it is realized that other factors may influence the intensity of the first sound, such as respiration, rate, length of diastole, and so forth, for reasons already pointed out, we do not feel, that they are of major importance in the changing first sound in auricular flutter. In fact, the respiratory effect was eliminated in the upper tracing of Fig. 12 as the phonocardiogram was taken while the breath was held in midexpiration. The same technique was employed in most of the other studies reported here. We believe, as has been emphasized by Dock,[7,8] that the first heart sound is predominantly, if not entirely, valvular in origin, and is dependant to a great extent on the position of the A-V valves at the moment of ventricular systole. When the auricles contract just before the ventricles, the A-V valves are necessarily in a different position (deeper in the ventricles) than if they contract a longer time before the ventricles, when they may have already receded from their low position. It is logical to assume that the loudness of the sound will differ with changes in the position, which will be reflected in changes in the P-R interval.

In Fig. 13 are shown four cases of auricular flutter with changing intensity of the first sound. One might speculate that the first two cases resemble paroxysmal auricular tachycardia with block, but a study of other tracings, particularly during carotid sinus stimulation, made us regard them as instances of auricular flutter. Changing first sounds were noted in each of the four cases. Fig. 14 illustrates a case of 2:1 flutter with a changing first sound. Although the basic rhythm was 2:1 block, the ventricular response was not perfectly regular. Conduction to the ventricles from the perfectly regular auricles was not absolutely constant with each second cycle. The correct diagnosis of this case was made at the bedside on the basis of the auscultatory findings and the response to carotid sinus stimulation.

In addition, we have observed two cases of paroxysmal auricular tachycardia with block, apart from the two questionable cases illustrated in Fig. 13, which also showed changing first sound (Fig. 15). As in flutter, the "P-R" relationship was an apparent major factor. In fact, one would suspect that the findings in paroxysmal auricular tachycardia with block and auricular flutter would be alike in this respect, because of the underlying similarity of the two mechanisms.

In addition to the changing first sound, occasionally one may hear "extra" sounds during the cardiac cycle which correspond to auricular contractions.

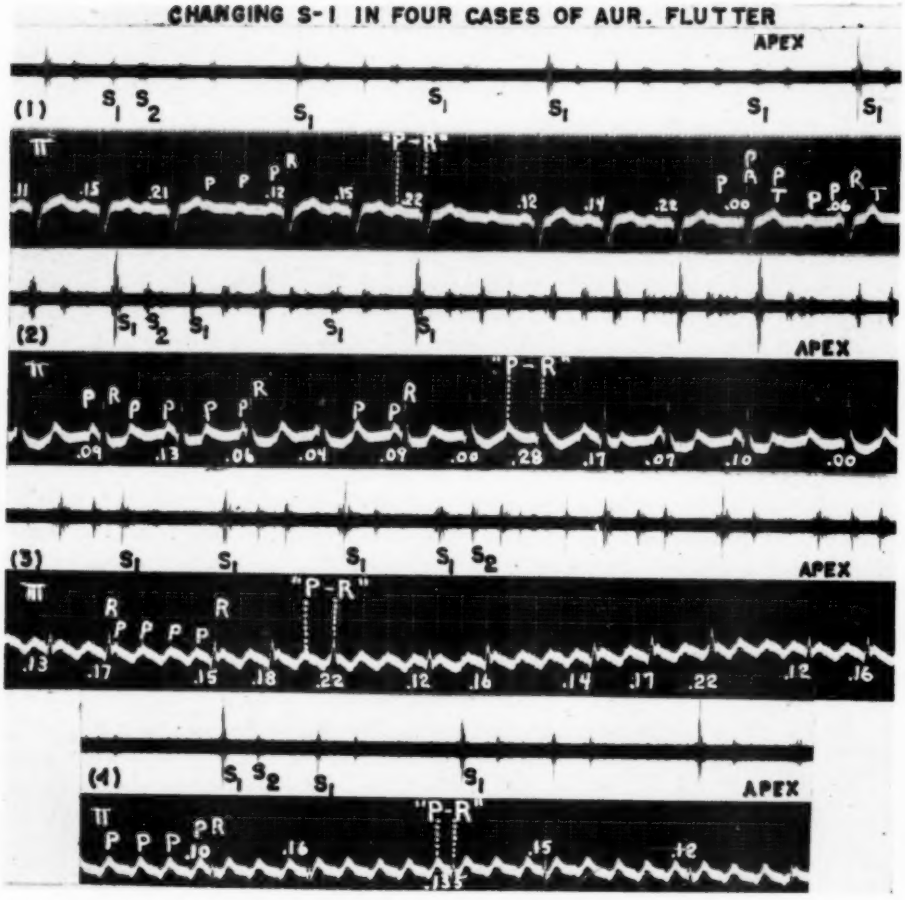


Fig. 13.—Four cases of auricular flutter showing changing first sounds (S_1). Note that the "*P-R*" interval in all cases is measured from the peak of the "*P*" wave. The loud first sounds occur in a "*P-R*" range of .06 to .12 second in the first case, .06 to .10 second in the second case, .22 second in the third case, and .10 to .13 second in the last case.

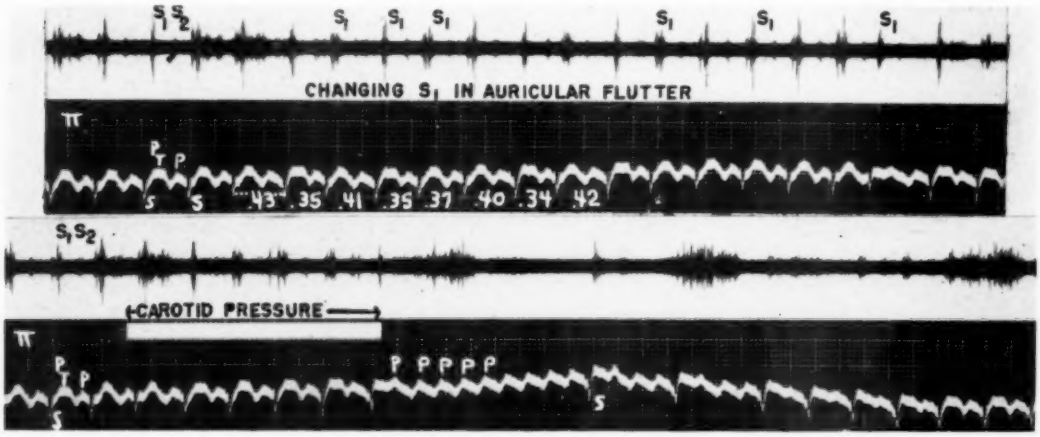


Fig. 14.—Man, 56 years of age, with 2:1 flutter following myocardial infarction. Changing intensity of first sound (S_1) noted clinically. The S-S intervals are not perfectly regular. Carotid pressure in lower tracing brings out the auricular waves (*P*).

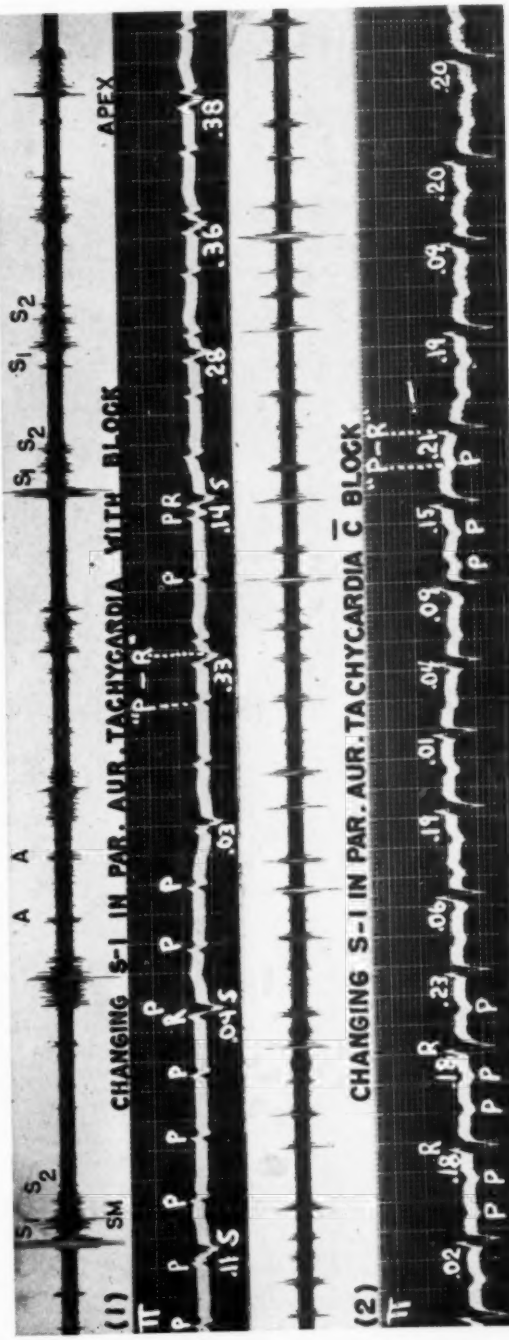


Fig. 15.—Two cases of paroxysmal auricular tachycardia with block. In upper tracing, note the marked change in intensity of the first sound, loud when the "*P-R*" range is .11 to .14 second. Auricular sounds (*A*) also noted. "*P-R*" interval in this case measured from peak of P to bottom of S. Lower tracing shows loudest first sound (S_1) when "*P-R*" is .06 to .09 second.

Such auricular sounds in flutter have been described and photographed by previous observers.[9,10] The sounds may appear during systole (between the first and second normal sounds) or in different parts of diastole (Fig. 16). In one instance, the extra sounds were so prominent that they made some observers believe auricular fibrillation was present, though the true ventricular rate was rather slow and almost regular.

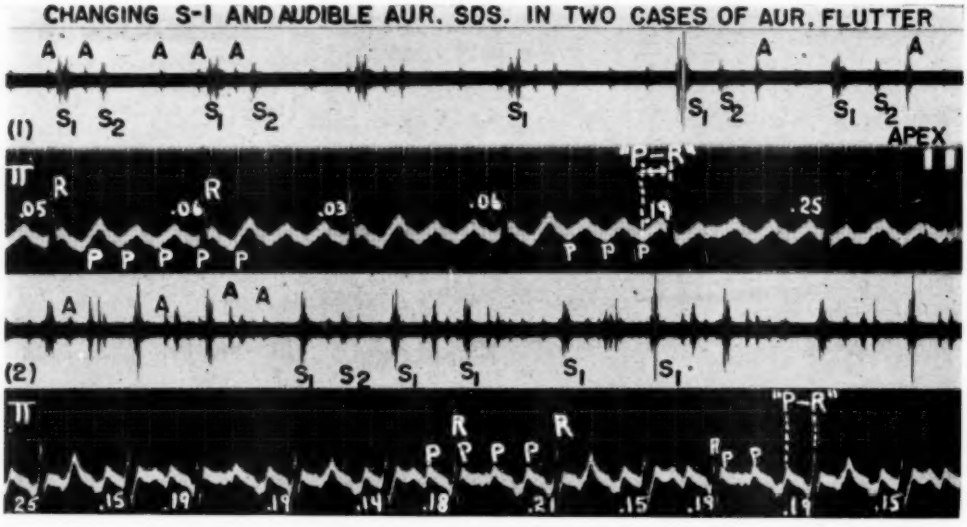

CHANGING S-1 AND AUDIBLE AUR. SDS. IN TWO CASES OF AUR. FLUTTER
A A A A A
A A
(1) S1 S2 S1 S2 S1 S1 S2 S1 S2
APEX
"P-R"
R R
.05 .06 .03 .06 .19 .25
P P P P P P P P
A A A A
A A
(2) S1 S2 S1 S1 S1 S1
"P-R"
R R
P P P P P P P
.25 .15 .19 .19 .14 .18 .21 .15 .19 .19 .15

Fig. 16.—In upper tracing note almost regular rhythm with marked increase in intensity of the first sound (S_1) when "*P-R*" is .19 second. Audible auricular sounds (*A*) occur during systole (between S_1 and S_2) as well as during diastole (S_2—S_1). Note auricular sounds in last two complexes are louder than second sound (S_2). Woman, 32 years of age, with rheumatic heart disease. Lower tracing (Case 2): "*P-R*" range of .14 to .15 second results in loudest S_1. Audible auricular sounds also present in systole and diastole. Basic rhythm irregular. Man, 60 years of age, with rheumatic heart disease.

We believe that the auscultatory findings which have been discussed serve as an added aid to the bedside diagnosis of auricular flutter. They should prove valuable, especially when coupled with the other previously established methods of diagnosis. Although resort to the electrocardiograph may at times be indispensible in obtaining final proof, these simple signs may often enable the observer at least to suspect the presence of auricular flutter and at times to make a fairly definite clinical diagnosis.

SUMMARY

A new auscultatory sign has been observed in auricular flutter; changing intensity of the first heart sound. This phenomenon was present in eight cases where the ventricular response was irregular, although in some the degree of irregularity was very slight. In two instances where the rhythm was perfectly regular the first sound was essentially constant. It is thought that the changing intensity of the first sound is a result of a variation in the P-R interval similar

to the mechanism of the changing intensity of the first sound in complete A-V block and ventricular tachycardia.

These observations support the hypothesis that the first heart sound is mainly, if not entirely, valvular in origin and is dependent to a great extent on the position of the A-V valves at the moment of ventricular systole, a concept proposed by Dock.

Other factors, such as respiration and length of diastole, which may influence the intensity of the first sound, were found not to be responsible for the alterations observed in this study.

Two cases of paroxysmal auricular tachycardia with block were also observed which showed a changing intensity of the first sound, the mechanism being similar to that of flutter.

Other methods that aid in bedside diagnosis are the slowing effect following carotid sinus stimulation or deep breathing, particularly when there follows a jerky or irregular retreat to the original rate, the effect of exercise which may exactly double the heart rate or temporarily cause the irregular rhythm to become rapid and regular, and the detection of additional "auricular" sounds coming in different parts of diastole and even during systole.

These new auscultatory findings, coupled with other bedside methods of examination, have been very helpful in the clinical diagnosis of auricular flutter.

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OXYGENATION STUDIES IN CONGENITAL PULMONARY STENOSIS

An Application of Recording Oximetry in the Evaluation of Cardiorespiratory Function

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RECENTLY the Blalock-Taussig operation[1-4] has been performed in fourteen cases of tetralogy of Fallot at this hospital. Physiologic studies of pulmonary oxygenation were made in ten of these patients by means of recording oximetry, of which two representative cases are presented. The studies were carried out preoperatively, during surgery, and postoperatively. The data obtained afford a convenient measure of cardiorespiratory function. Consequently, the method should be useful for assaying the benefit derived from the operation. In addition, the recorded changes in the arterial oxygen saturation during surgery offer a valuable adjunct to the surgeon and to the anesthetist.

METHODS

The Millikan-Smaller oximeter,[5,6] together with suitable recording apparatus described by Hemingway,[7,8] was used to obtain continuously the relative changes in the patient's arterial oxygen saturation. Arterial blood was drawn at appropriate intervals during the oximetry to obtain absolute blood oxygen values for calibration of the oximeter tracings. This precaution is advisable, particularly in cyanotic patients, because of the lesser accuracy of oximetry in the lower saturation ranges.[5]

In the preoperative studies, the effects on the arterial oxygen saturation were determined under the following conditions: (1) altering the tension of oxygen in the inspired air (using room air and 100 per cent oxygen), and (2) standardized exercise.

During surgery, the patient's oxygenation was recorded throughout the period of anesthesia.

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Postoperatively, a similar procedure was carried out as in the preoperative test. Exercise was extended to obtain a significant effect on the saturation. For twelve hours prior to the tests the patient was kept in bed to insure a basal state.

CASE REPORTS

CASE 1.—An 11-year-old white boy, D. A., was admitted to University Hospitals on Sept. 18, 1946, with a history of cyanosis that had been noticed since the age of 5 years. During the past six years, the child's physical endurance had progressively decreased, cyanosis had become severe, and digital clubbing had developed. Within the three-week period prior to admission, the patient had several episodes of syncope and orthopnea. At the time of admission, the patient was able to walk only fifty feet before he was forced to rest.

Physical examination revealed a poorly nourished, poorly developed boy with dyspnea at rest. A deep cyanosis was present in the nail beds and mucous membrances. The skin showed a dusky appearance with a prominent superficial venous pattern. There was suffusion of the conjunctivae. Marked clubbing was apparent in the fingers and toes. Examination of the chest revealed no enlargement of the heart as determined by percussion; the rate and rhythm of the heart were regular. The first heart sound was reduplicated and the second heart sound was pure. Along the left sternal border a soft blowing murmur was audible which was loudest in the second intercostal space. The blood pressure was 90/80 in each arm. There was no sign of cardiac decompensation.

Laboratory data showed a hemoglobin of 21.2 Gm., red blood cells of 8,700,000, and hematocrit of 80 millimeters. Arterial blood showed an oxygen content of 12.33 volumes per cent and an oxygen capacity of 30.82 volumes per cent (saturation, 40.9 per cent). The carbon dioxide capacity of venous blood was found to be 51 volumes per cent. Blood chlorides were 582 mg. per cent and blood urea nitrogen was 12 mg. per cent. Electrocardiography showed right axis deviation with spiked elevations of the P waves. By x-ray and fluoroscopy the cardiac index was found to be within normal limits. There was noted an absence of fullness of the pulmonary conus and the right ventricle appeared enlarged. The aortic arch was on the right side. The vascular markings in the lung fields appeared decreased. A diagnosis of tetralogy of Fallot was made, and on Sept. 20, 1946, the Blalock-Taussig operation was performed in which the left subclavian artery was anastomosed to the left pulmonary artery.

Oximetry Studies.—

Preoperative (Fig. 1,*A*): The basal blood oxygen saturation was 40.9 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 40.9 per cent to 45.0 per cent over a period of fifteen minutes. When the patient was exercised by walking, the saturation of blood oxygen decreased to 35 per cent within four minutes. At this time, because of the patient's distress, 100 per cent oxygen was administered, and seven minutes were required for the saturation to reach the previous basal level of 40 per cent.

Operative Record (Fig. 1,*B*): Following induction of anesthesia consisting of cyclopropane-oxygen, the patient's saturation was increased to a recorded value of 42 per cent. A slight decrease was noted in the saturation when the chest was opened. On several occasions, the percentage of oxygen in the anesthetic mixture had to be increased to prevent decreases in the saturation. When the left subclavian artery-left pulmonary artery anastomosis was completed and the clamps released, the saturation was only 42.6 per cent. Since a saturation increase of greater magnitude had been expected, the anastomosis was reinspected. Following probing of the anastomosis there was a rise in the recorded saturation to 47 per cent.

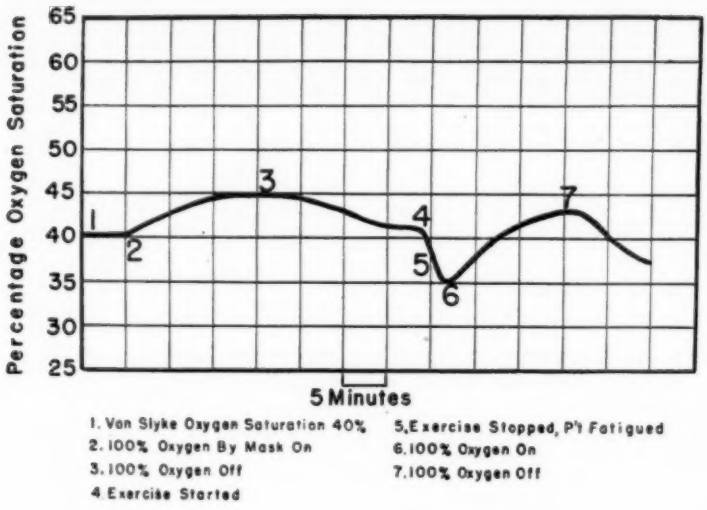

Fig. 1,*A*.—Case 1. Preoperative oximetry studies. See text for further description.

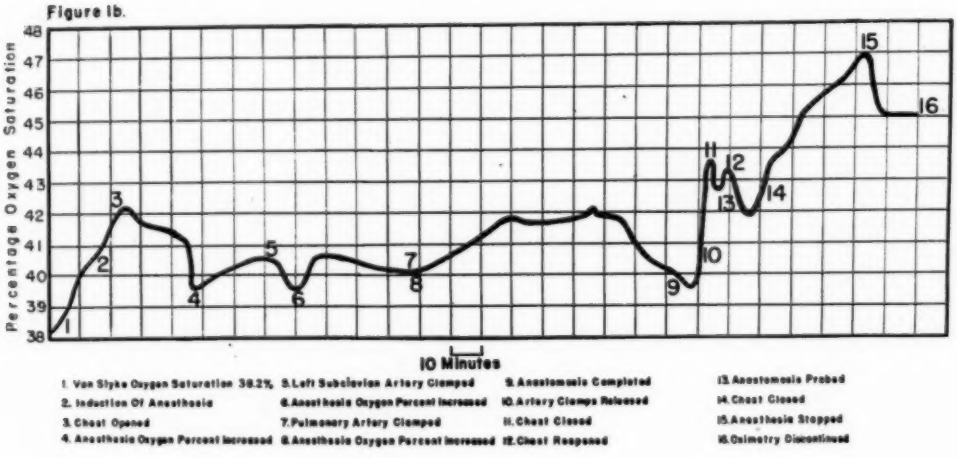

Fig. 1,*B*.—Case 1. Oximetry studies during operation.

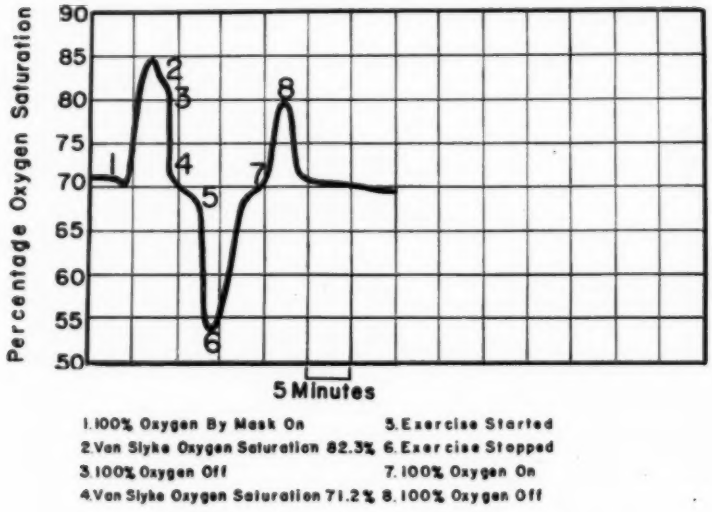

Fig. 1,*C*.—Case 1. Postoperative oximetry studies.

Postoperative (Fig. 1,*C*): This record was taken three months following operation. The basal blood oxygen saturation was 72 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 75 per cent to 85 per cent over a period of three minutes. When the patient was exercised as in the preoperative study, the saturation decreased to 53.5 per cent within two minutes. However, after five minutes of rest with the patient breathing air the saturation was restored to 70 per cent.

CASE 2.—A 5-year-old white girl, L. R., was admitted to University Hospitals on Sept. 30, 1946, with a history of cyanosis since birth. Since the age of 18 months, her condition had been diagnosed as congenital heart disease. She was able to take only a few steps before being forced to rest. There had been no episodes of unconsciousness.

Physical examination revealed the patient to be well developed and well nourished. The skin was plethoric and there was a deep cyanosis noted in the nail beds and mucous membranes. Moderate digital clubbing was present. Chest examination showed no cardiac enlargement to percussion, heart sounds were well heard, and no irregularities of cardiac rate or rhythm were found. Along the left sternal border a harsh systolic murmur and thrill were apparent with greatest intensity in the third intercostal space. Blood pressure was 104/84 in each arm.

Laboratory data revealed a hemoglobin of 26.5 Gm., red blood cells of 9,840,000, and hematocrit of 82 millimeters. Arterial blood showed an oxygen content of 15.4 volumes per cent and an oxygen capacity of 35.49 volumes per cent (saturation, 43.5 per cent). Electrocardiography showed right axis deviation and spiked elevations of the P waves. By x-ray and fluoroscopy the cardiac index was found to be within normal limits. A concavity was noted along the left cardiac border, and there was right ventricular hypertrophy. The aortic arch and descending aorta were on the right side. A diagnosis of tetralogy of Fallot was made, and a Blalock-Taussig operation was performed on Oct. 3, 1946, at which time the innominate artery was anastomosed to the left pulmonary artery.

Oximetry Studies.—

Preoperative (Fig. 2,*A*): The basal blood oxygen saturation was 45.9 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 45.9 per cent to 65.0 per cent over a period of ten minutes. Exercise test was unsatisfactory because the patient was in severe distress upon slight exertion. When 100 per cent oxygen was withdrawn and the patient allowed to breathe room air, twenty minutes were required for the saturation to decrease to the previous basal value of 45 per cent.

Operative Record (Fig. 2,*B*): Following induction of cyclopropane-oxygen anesthesia, the saturation reached a recorded value of 67 per cent and remained above 60 per cent until the pulmonary artery was clamped. At this juncture the recorded saturation decreased to 55 per cent. Following completion of the innominate artery-left pulmonary artery anastomosis, removal of the clamps was followed by an increase in the recorded saturation to 71 per cent. At this time the patient developed peripheral vascular collapse suddenly, and the saturation decrease accompanying this shock was rapidly reversed by the administration of the intravenous plasma and 100 per cent oxygen.

Postoperative (Fig. 2,*C*): This record was taken five months following operation. The basal blood oxygen saturation was 78 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 78 per cent to 88 per cent over a period of two and one-half minutes. When the pa-

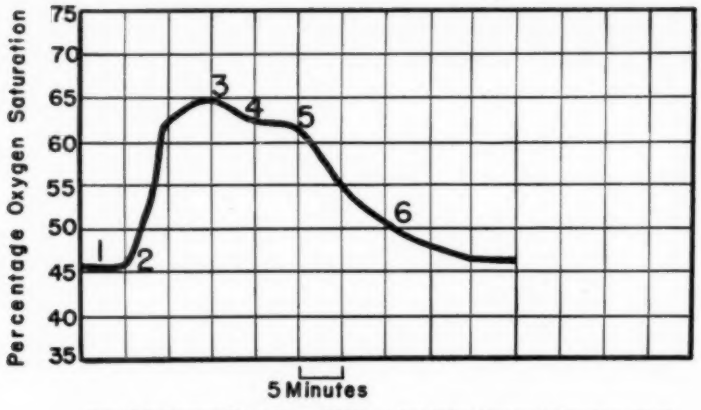

Fig. 2,*A*.—Case 2. Preoperative oximetry studies. See text for further description.

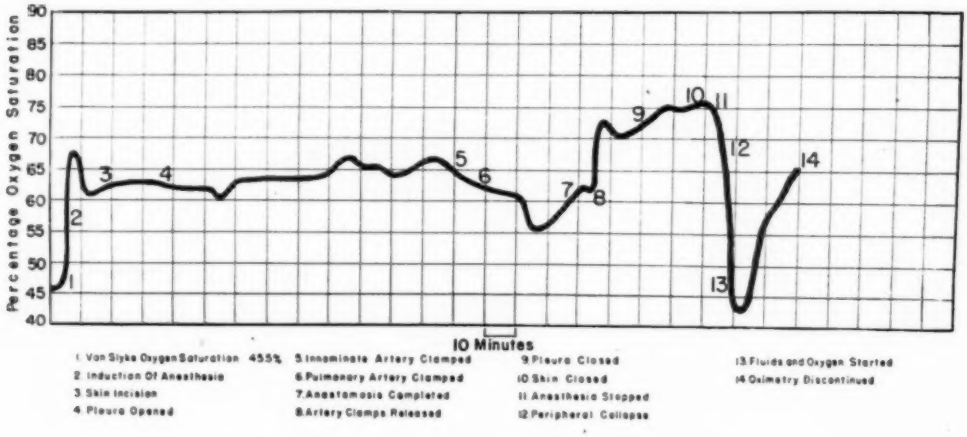

Fig. 2,*B*.—Case 2. Oximetry studies during operation.

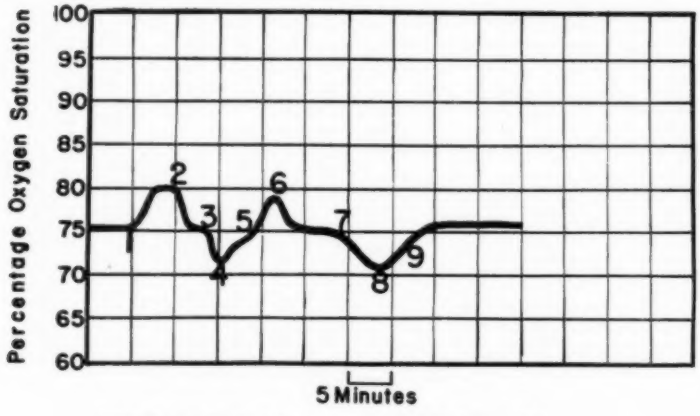

Fig. 2,*C*.—Case 2. Postoperative oximetry studies.

tient was exercised by walking, there was a decrease in the recorded saturation to 73 per cent within two minutes, and three minutes were required for the saturation to return to 78 per cent with the patient breathing room air.

DISCUSSION

The recording oximeter is a valuable instrument for studying oxygen saturation changes under various circumstances in patients with cyanotic congenital heart disease. To obtain the descriptive curves of the saturation responses by chemical analysis of arterial blood samples would be difficult, if not impossible, because of the many arterial punctures required. Because the physiologic adjustment postoperatively depends primarily upon the efficiency of the heart and lungs in supplying oxygen to the tissues, oximetry is an excellent method for obtaining this information directly. The complexity of vascular mixing in the cardiovascular system of these patients necessitates indirect measurement of cardiac output and total pulmonary flow postoperatively. Although oximetry does not provide these data quantitatively, the saturation responses furnish a valid measure of the success of the shunt operation.

It is believed that a very significant determination for evaluation of the operative success is the saturation time. This term refers to the time required to reach maximal arterial oxygen saturation when a subject is breathing 100 per cent oxygen. Recently, Fowler and Comroe[9] have utilized oximetry to determine this interval in normal subjects. Their results indicate saturation time within three minutes. It is, of course, well known that a normal individual can fully saturate his arterial blood when breathing pure oxygen, while the average saturation is 97 per cent in the normal atmosphere. Preoperatively, in the cases studied in this series, the saturation time was prolonged three to four times over the normal, ranging from ten to fifteen minutes. Postoperatively, all patients were found to have saturation times within the normal range. More recently it has been possible to study three of Dr. Alfred Blalock's patients, who were six months, one year, and two years postoperative, respectively. All three reached maximal saturation within three minutes when breathing 100 per cent oxygen. It is significant, however, that the exercise tolerance postoperatively (in terms of the range of the saturation response) continues to indicate a limitation in the cardiorespiratory reserve function. This is not surprising when one remembers that the proportion of shunted blood increases appreciably with exercise. The last two mentioned patients, nevertheless, showed a maximal decrease in saturation of only five per cent with extended exercise.

The explanation of the increased saturation time preoperatively in these cases, as well as the return to normal postoperatively, is not clear at the present time. The remarkably great increment in peripheral oxygen saturation, which usually occurs in patients with tetralogy of Fallot while breathing 100 per cent oxygen, is equally difficult to explain.

One factor which has to be considered is an increased pulmonary capillary barrier. It is difficult to state whether or not a gradient between the alveolar oxygen tension and the oxygen tension in the pulmonary vein exists. However,

blood obtained from the pulmonary vein by catheterization in several cases of tetralogy of Fallot has shown an oxygen saturation of from 95 to 97 per cent. Therefore, this aspect is felt to be of no great importance in the present consideration.

Another important factor to be considered is the mixing of venous blood and fully saturated pulmonary venous blood in the right ventricle and aorta. If one assumes that the arteriovenous difference remains essentially constant, the arterial oxygen content could rise slowly, as a result of a gradual increase to a maximal level of the oxygen content of the mixed venous blood. To correlate this suggested hypothesis with the facts obtained by the oximeter, it will be necessary to obtain more simultaneous data.

The normal saturation time postoperatively must be related to the increased "effective pulmonary blood flow," which has been demonstrated by Bing, Vandam, and Gray.[16]

It is worthy of note that the two patients presented in detail responded differently to 100 per cent oxygen. Preoperatively, Patient 1 showed a rise of only 5 per cent in oxygen saturation, while Patient 2 rose 20 per cent. Postoperatively, Patient 1 rose 15 per cent, while Patient 2 rose only 10 per cent. However, both demonstrated the same changes in saturation time (which became normal after surgery) while being prolonged preoperatively. Oximeter studies on a greater number of patients will perhaps clarify this discrepancy or variability in range of maximal saturation attained when 100 per cent oxygen is administered.

CONCLUSIONS

The studies on arterial oxygen saturation reported at this time show two important facts. First, the rise in arterial oxygen saturation upon the establishment of the systemic-pulmonary arterial shunt was practically immediate; and second, the saturation time upon administration of 100 per cent oxygen was greatly shortened following surgery. The first observation indicated that the shunt had a direct primary beneficial effect on arterial oxygen saturation. The second would seem to show that the net effect of the operation was to increase the fraction of the total cardiac output supplying the pulmonary vascular bed. The implication from these observations is that the shunt resulted in a substantial improvement in the functional capacity of aeration of blood.

SUMMARY

1. The recording oximeter has been used to measure changes in arterial oxygen saturation in ten cases of tetralogy of Fallot. Detailed studies of two cases are presented.

2. The observations have shown immediate increase in arterial oxygen saturation and decrease in the saturation time after establishment of a systemic-pulmonary arterial shunt.

3. The significance of alterations in the saturation time has been discussed and a possible explanation presented.

4. The recording oximeter provides instantaneous information concerning arterial oxygen saturation during the course of surgical procedures involving the great vessels, and can provide the surgeon and anesthetist with valuable guides as to the condition of the patient during anesthesia.

We are indebted to Dr. M. B. Visscher, Dr. Allan Hemingway, and Dr. Irvine McQuarrie for their helpful advice and cooperation.

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WOLFF-PARKINSON-WHITE SYNDROME WITH MYOCARDIAL INFARCTION: AN EXPERIMENTAL STUDY

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THE Wolff-Parkinson-White syndrome, which shows an electrocardiographic pattern consisting of a short P-R interval associated with a wide QRS complex and abnormal T waves, has been recognized commonly in the past few years, and many case reports have appeared in the literature. More recently there have been several reports of the Wolff-Parkinson-White syndrome associated with myocardial infarction,[1-3] which is the subject of this paper.

METHODS

The experimental work was performed on cats according to a procedure previously outlined.[4,5] In brief, this consists of picking up the auricular excitation wave by electrodes placed directly upon the right auricle in the open chest of a cat, amplifying these impulses, and passing them into a time-delay circuit. The output of the time-delay circuit is then used to stimulate the ventricles. In this manner an electrical short circuit between the auricle and ventricle is established by which any desired degree of premature stimulation of one ventricle can be accomplished; in other words, ventricular fusion beats are produced.

The term ventricular fusion is used to indicate excitation of the ventricles by two or more stimuli originating in different parts of the heart at approximately the same time and each causing contraction in a limited area of cardiac muscle. In the present work part of the ventricles are stimulated by the normal conduction system and part by the extra stimulus introduced prior to the time the ventricle is stimulated in the normal manner. The degree of fusion is thus a function of the prematurity of the artificial stimulation. If the artificial stimulus falls too early, all the ventricular muscle will be stimulated from this source alone, and the resultant beat will be a simple premature ventricular contraction. With proper timing of the premature artificial stimulus any desired degree of fusion may be obtained. In the present work fusion was studied before and after ligation of a coronary artery.

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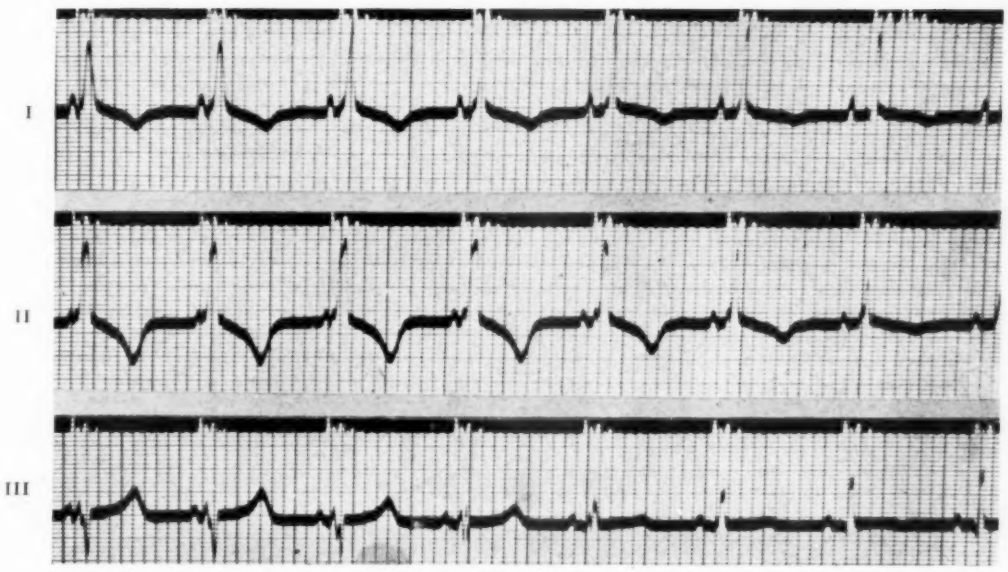

Fig. 1.—Cat No. 5. Fusion produced by variable pre-excitation of the right ventricle in the undamaged cat heart. On the right side are normal beats, while those on the left are premature ventricular contractions. Varying fusion is produced by gradually changing the amount of delay of the circuit stimulating the right ventricle. From the left to right there is a gradual increase in the P-R interval, a gradual narrowing of the QRS complex, and a gradual change in the magnitude of the QRS complex and the T waves, which is the result of ventricular fusion.

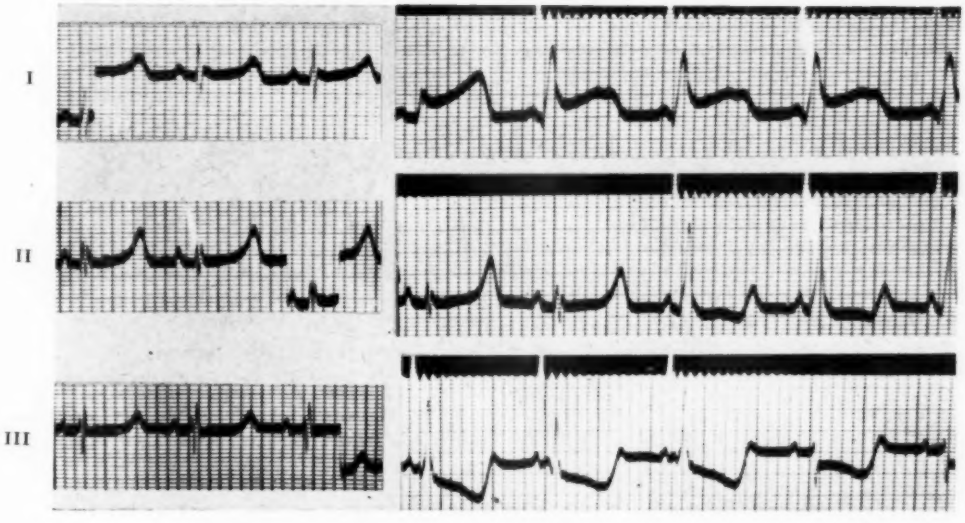

Fig. 2.—Cat No. 2. On the left are seen the standard leads before ligation of the anterior descending coronary artery in a cat. On the right side are the same leads after ligation. The break in the black line at the top of each tracing indicates the time of excitation of the right ventricle. Normal beats are present in each lead (Complex 1 in Lead I, Complexes 1 and 2 in Lead II, and Complex 4 in Lead III).

EXPERIMENTAL RESULTS

Fig. 1 shows fusion beats produced by variable pre-excitation of the right ventricle in the undamaged cat heart. With variation in the P-R interval, changes in the duration and character of the QRS and T waves are produced. These changes are the result of varying degrees of ventricular fusion.

Fig. 2 shows the standard leads before and after the ligation of the anterior descending coronary artery at a point midway between the apex and base of the heart. The ligation of this artery produced an anterior myocardial infarction involving the apex of the left ventricle which was grossly evident. Fusion was accomplished an hour after the ligation by premature stimulation of the right ventricle. Inspection of the record reveals that fusion produces rather marked changes in the configuration of the electrocardiogram, but the pattern of acute myocardial infarction with S-T segment changes is partially preserved.

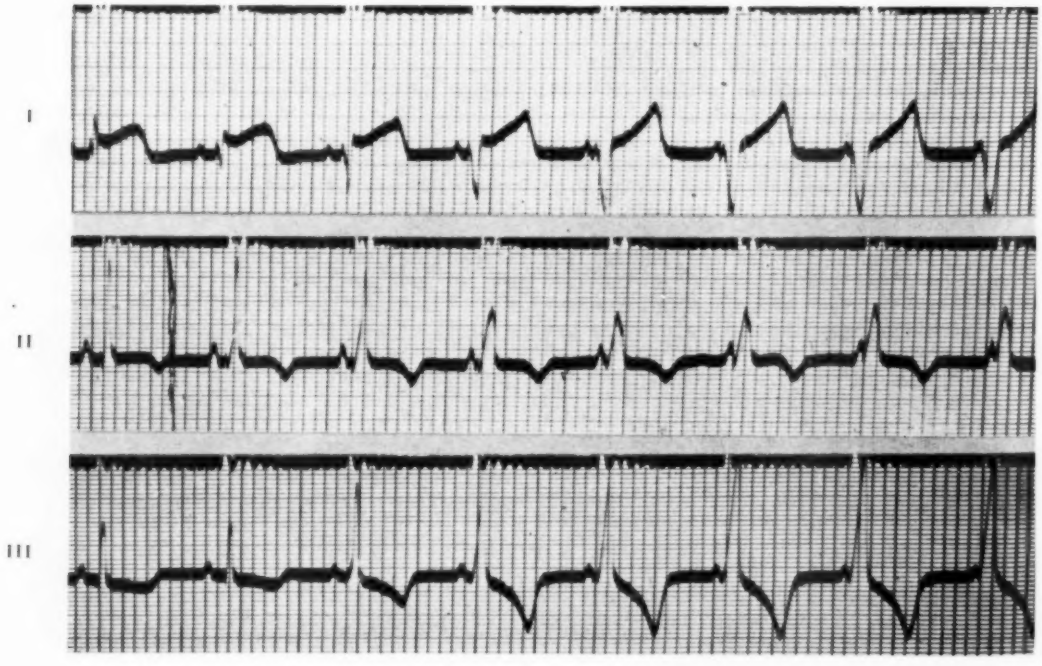

Fig. 3.—Cat No. 5. Variable fusion produced by pre-excitation of the left ventricle after ligation of the anterior coronary artery. The first beat in each lead is a normal complex and shows the acute changes of myocardial infarction. The following beats are fusion beats with a gradual transition to the form of a pure ventricular extrasystole. See Fig. 1 for normal electrocardiogram of same animal.

Fig. 3 shows fusion produced by pre-excitation of the left ventricle after ligation of the anterior coronary artery in the same position. Here the pattern of the myocardial infarction is difficult to recognize in the fusion beats, in contrast to the previous electrocardiogram where pre-excitation of the right ventricle was produced.

DISCUSSION

Inspection of the records reproduced in recent articles of Wolff-Parkinson-White syndrome with myocardial infarction indicates that in no case were there definite clear-cut changes indicative of a large full-thickness infarct with Q-wave and S-T segment changes. Some records showed inversion of the T waves for a period of days or weeks, combined with a clinical history suggestive of acute myocardial infarction. It is known that changes in the character of the T wave may occur in the Wolff-Parkinson-White syndrome which are the result of varying degrees of fusion. Such changes are illustrated in Fig. 4, taken from a human case. The changes in the QRS complex and T waves are seen in all leads, but particularly in Lead III. Such changes in the T wave, due to variable fusion, are very difficult to differentiate from T-wave changes due to underlying myocardial pathology. In addition, Wendkos and Nadler[6] have recently shown that instability of the T waves, as seen in cases of neurocirculatory asthenia, can occur in patients showing a Wolff-Parkinson-White syndrome.

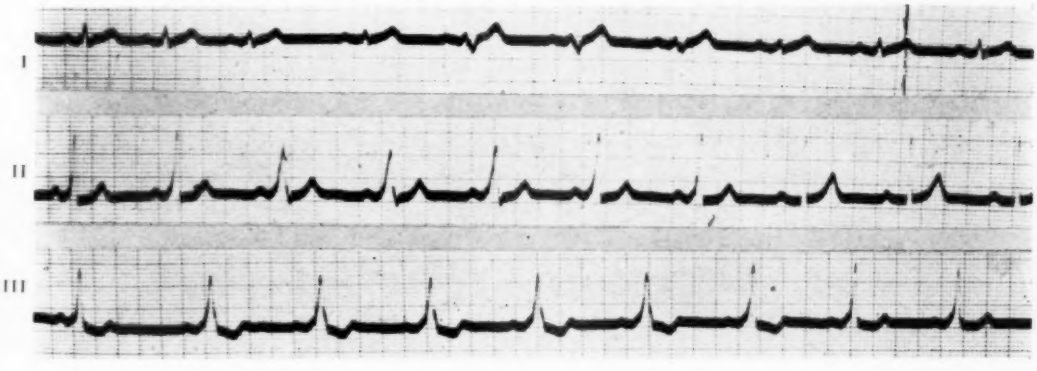

Fig. 4.—A human case showing variable fusion. A few normal complexes can be seen in Leads I and II, but all complexes in Lead III show the Wolff-Parkinson-White syndrome. Variations in the character of the abnormal complexes are apparent.

Our experimental findings indicate that it should be possible to diagnose a large infarct, particularly during the acute stage when changes in the S-T segments are prominent. It seems to us, however, that changes in the T waves alone would be very difficult to evaluate in the presence of a Wolff-Parkinson-White syndrome. This problem is similar to the difficulty encountered in the diagnosis of myocardial infarction in the presence of bundle branch block, expecially in left bundle branch block where, at times, it is difficult or impossible to establish the diagnosis of myocardial infarction.

The diagnosis of myocardial infarction in the presence of Wolff-Parkinson-White syndrome would be much more easily established if the syndrome pattern could be abolished. We suggest that in such cases an attempt should be made to convert the Wolff-Parkinson-White pattern to a normal mechanism. In our hands, the use of quinidine[8] has been satisfactory for this purpose; other measures are, at times, successful.

SUMMARY

An experimental study is reported which indicates that the diagnosis of acute myocardial infarction in the presence of Wolff-Parkinson-White syndrome can usually be established if the infarct is large and particularly if the right ventricle is prematurely stimulated. However, in small infarcts producing only T-wave changes, it is doubtful whether the electrocardiographic findings would be sufficient to establish a definite diagnosis of myocardial infarction. It is suggested that an attempt be made to convert the Wolff-Parkinson-White patterns to a normal conduction mechanism when myocardial infarction is suspected.

The authors wish to acknowledge the able technical assistance of Mr. Clarence E. Peterson.

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CARDIAC VIBRATIONAL INTENSITY AND CARDIAC OUTPUT

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RECENTLY we[1] reported in this JOURNAL a somewhat detailed study of the low-frequency vibrations which accompany each heart beat. It was shown that the major portion of the intensity of such vibrations is contributed by the fundamental (that is, the frequency of the individual beat) and its harmonics up to about the fifteenth. During each heart beat the relative intensities of individual harmonics change in a regular fashion. Harmonic analyses of cardiac vibrations were used to support the hypothesis that the "mean" harmonic of the intensity-frequency distribution, calculated over successive short intervals of the heart cycle, is related in a simple manner to the rate of change in length of ventricular muscle fibers and, therefore, to the rate of change of ventricular volume. By summing these "mean" harmonics, a curve was produced similar to the ventricular volume curve recorded directly by Wiggers.[2]

Our original study of cardiac vibrations required elaborate apparatus and tedious calculations. Further study has been simplified by construction of an apparatus which we term a "Heart Sound Meter" (H.S.M.), which converts, by electronic means, the complex vibrations picked up at the chest wall into a factor analogous to the "mean" frequency of the intensity-frequency distribution and finally integrates this factor. A record of the output of the heart sound meter, made on such a recording device as the General Electric Photo-Electric Recorder or photographed from the movements of a microammeter in the heart sound meter itself, traces during each heart beat a curve like that of ventricular volume. The coordinates of this curve are time, on the horizontal axis, and a function which we term "resultant frequency" on the vertical axis. (We use the term "resultant frequency" because our apparatus has converted the complex signal of cardiac vibrations picked up at the chest wall into a signal which could be produced at each instant in the heart cycle by presenting a single sine wave signal to the apparatus. The frequency of this simple signal would vary from instant to instant.)

The similarity of the pattern of the heart sound meter output to the ventricular volume curve at once suggested the possibility of using the meter to determine cardiac output. This use is discussed in the present report.

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The most convenient method for determining stroke volume to check heart sound meter records is the ballistocardiograph. In our present study, we used a high-frequency apparatus constructed after the design of Dr. H. A. Blair, of the Department of Physiology, University of Rochester, N. Y.* The oscillations of the bed were converted into electrical energy by a crystal pick-up and recorded on the electrocardiograph channel of the Sanborn Stetho-Cardiette. Stroke volumes were calculated by Starr's[3] formula, $S_v = 11\sqrt{(I + J)\, C^{3/2}\, A}$, the amplitude of deflections, I and J, being converted to the sensitivity of Starr's bed by use of the specific constant of our bed and a factor for the sensitivity of the Sanborn Stetho-Cardiette.

COMPARATIVE STUDIES MADE WITH THE HEART SOUND METER AND BALLISTOCARDIOGRAPH

Records made with the ballistocardiograph were compared with heart sound meter records in two ways, which are illustrated by Figs. 1 and 2.

(1) The electrocardiograph and heart sound meter were synchronized, and the heart sound meter output was recorded directly on a General Electric Photo-Electric Recorder. For comparison, a number of successive heart cycles (usually ten) were measured. The records on the Photo-Electric Recorder were adjusted for the slight lack of linearity of the recorder and for the period of the recorder galvanometer.

(2) The heart sound meter data were read from two microammeters, one recording the smoothed "resultant frequency" of some three successive heart cycles and the other showing a function of the "range," that is, the amplitude of each cycle. It was most convenient, in practice, to set this second meter to read the square of the range again smoothed over some three successive beats. While these meters were being read, ballistocardiograph records were made on the Sanborn Stetho-Cardiette and ten successive heart cycles measured to give an average stroke volume.

The general formula for calculation of stroke volume from the heart sound meter is

$$S_v = 2\ \Delta f.\ \bar{f}$$

when Δf is the range and $\bar{f}$ the mean "resultant frequency." This may also be written

$$S_v = f_1^2 - f_2^2$$

where f_1 is the maximum and f_2 the minimum "resultant frequency" in the systolic phase of each heart cycle. This formula is derived from

$$S_v = 2\Delta f.\bar{f} = 2(f_1 - f_2)\frac{(f_1 + f_2)}{2} = f_1^2 - f_2^2$$

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*We wish to thank Dr. W. O. Fenn, Professor of Physiology, University of Rochester, N. Y., for diagrams of the Blair ballistocardiograph.

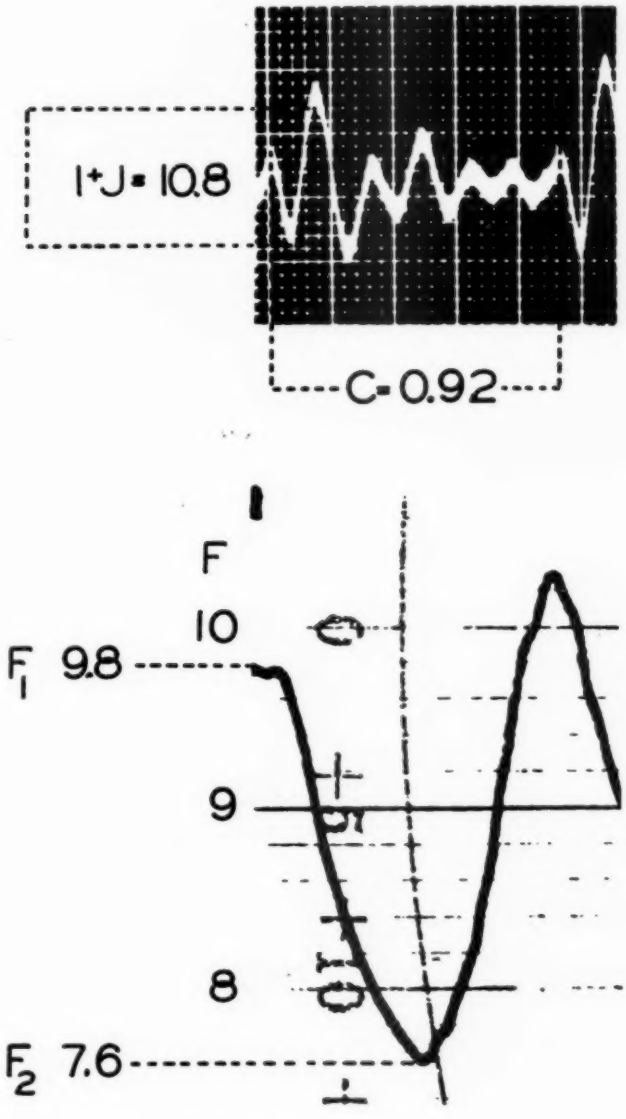

Fig. 1.—Above: Ballistocardiograph record

$$S_v = 11K\sqrt{(I+J)C^{2/2}A} = 53 \text{ c.c.}$$

when

K = constant for bed and recorder sensitivity = 0.988
$A = 2.5$
$C^{2/2} = 0.885$
$(I + J) = 10.8$ mm.

Below: Heart sound meter record for same heart beat (made on General Electric Photo-Electric Recorder).

$$S_v = K_1 (f_1^2 - f_2^2) = 52 \text{ c.c.}$$

when

K_1 = constant for recorder galvanometer = 1.35
$f_1 = 9.8$ c.p.s.
$f_2 = 7.6$ c.p.s.

Stroke Volume During Rest.—The use of the ballistocardiograph as our standard was limited to resting conditions. Records taken immediately after exercise were apt to show abnormal forms. Starr took such forms into consideration by varying his "constant" from 11 to 15, apparently leaving the choice largely to

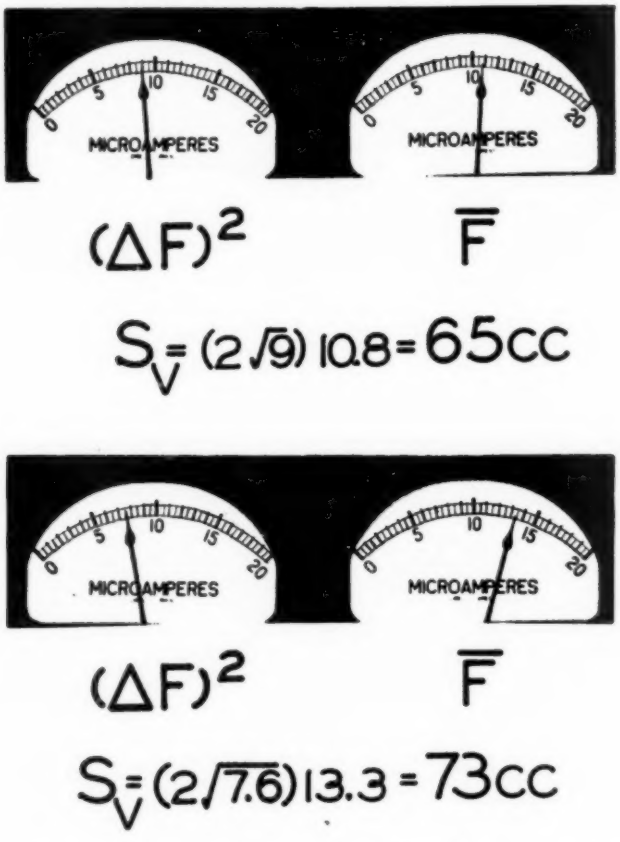

Fig. 2.—Direct calculation of stroke volume from heart sound meter. Left meter records square of range = $(\Delta f)^2$; right meter records mean frequency = $\bar{f}$. $S_V = 2\Delta f.\bar{f}$. Upper record taken immediately before Master 2-Step exercise test. Lower record taken immediately after exercise test.

the observer. For comparison of two methods of measuring cardiac output, based upon quite different principles, such a procedure appeared of doubtful value, since by simply varying a "constant" one might force the data to a spurious correlation.

Resting stroke volumes measured by the two procedures are plotted in Fig. 3. The limits of variability of the ballistocardiograph record accepted by Starr in comparison with the ethyl-iodide technique, ± 14.3 per cent, are indicated. None of the heart sound meter measurements falls outside this range. The coefficient of correlation between data given by the two methods is 0.95, with a standard error of less than ± 0.02. Recently, Nickerson, Warren, and

Brannon[4] have recorded a range of ± 25 per cent in comparing stroke volumes determined by the Fick principle, after right atrial catheterization, with those calculated from the low-frequency ballistocardiograph. They ascribe most of the deviation to unavoidable errors in the Fick technique. Stroke volumes determined by our heart sound meter would appear to be reasonably comparable to those found by other methods, at least under resting conditions.

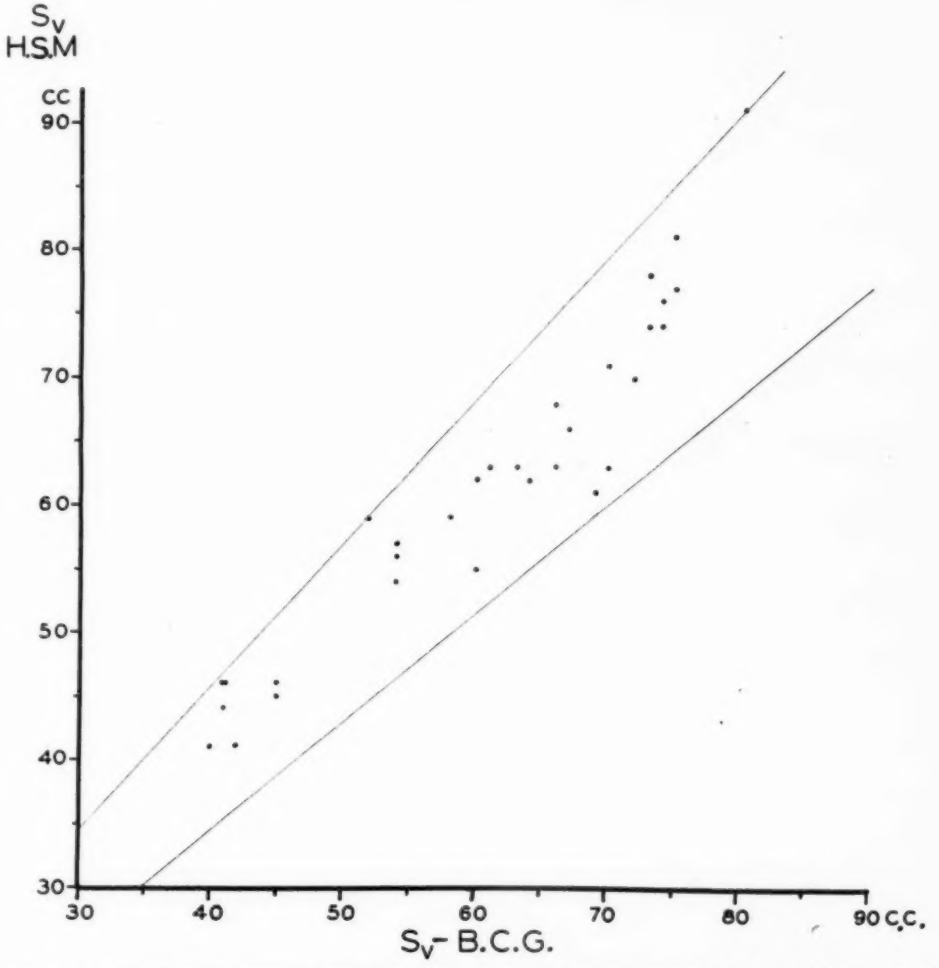

Fig. 3.—Comparison of stroke volumes calculated from ballistocardiograph (B.C.G.) and heart sound meter (H.S.M.). Diagonal lines limit ballistocardiograph ± 14.3 per cent.

Cardiac Output After Moderate Exercise.—To demonstrate the use of the heart sound meter in measuring cardiac output in conditions other than rest when the high-frequency ballistocardiograph might prove unsuitable, we made measurements before and after a series of moderate exercises reported by Grollman[5] in his classical monograph. Using the acetylene method with a quite elaborate analytical procedure, he was unable to make determinations of stroke

volume as frequently as they can be made with our meter. Table I gives comparative data. Since Grollman does not state how soon after exercise he made his determinations, we have given heart sound meter measurements made immediately (within about twenty seconds) and one or two minutes later. The direction of trend of cardiac output is the same for our tests as for Grollman's.

TABLE I. INFLUENCE OF MILD EXERCISE UPON CARDIAC OUTPUT. COMPARISON OF HEART SOUND METER DATA WITH DATA FROM GROLLMAN[5]

	GROLLMAN	CARDIAC OUTPUT: L./MIN. "HEART SOUND METER" TIME AFTER EXERCISE	C. O.
Resting	4.1	Resting	3.7
Flexing and extending right forearm, once per second	4.8	Immediately	4.7
		1 minute	3.7
Flexing right forearm rapidly	6.0	Immediately	5.0
		2 minutes	3.6
Alternately flexing and extending both forearms, each and every other second	4.3	Immediately	5.1
		1 minute	3.6
Flexing right thigh, once per second	7.7	Immediately	6.0
		1 minute	3.8
Alternately flexing both thighs, each every other second	5.0	Immediately	6.3
		0.5 minute	5.9
		1 minute	3.4

TABLE II. INFLUENCE OF ANOXIA UPON CARDIAC OUTPUT

TIME (MIN.)	EXPERIMENT 1	OX-IMETER %	PULSE RATE	C. O. L./MIN.	TIME (MIN.)	EXPERIMENT 2	OX-IMETER %	PULSE RATE	C. O. L./MIN.
0	Resting	98	60	4.44	0	Resting	98	65	5.10
2	Resting	98	60	4.52	3	Resting	98	64	5.41
4	Resting	98	60	4.52	6	Resting	99	66	4.88
6	Resting	98	62	4.56	9	Resting	98	64	4.83
7	Resting	98	60	4.50	11	Nitrogen on	98	64	4.74
8.5	Nitrogen on				13		95	66	4.26
9		99	66	5.39	16	Nitrogen increased	90	78	4.18
11		98	60	4.30	18	Nitrogen increased	85	80	6.14
12.5	Nitrogen					Nitrogen			
15	increased				21	increased	80*	82*	4.96
13.5		95	70	5.38	23		78*	82*	6.10
15		94	68	4.33	24		77*	82*	6.61
17	Nitrogen increased	91	74	5.48	25		73*	84*	6.21
19		89	76	6.26	26	Nitrogen off			
21	Nitrogen off	86	74	7.30	27		94	66	6.72
23		93	66	5.23	29		96	60	4.49
24		94	62	4.76	30		96	60	4.08
25		95	64	4.66	31		96	56	4.01
27		96	62	4.75					

*Oximeter galvanometer and pulse rate fluctuating widely with respiratory cycle.

Cardiac Output in Anoxia.—The influence of anoxia was studied by allowing our subjects, after a control period, to breathe air into which nitrogen was fed in increasing concentration. Instead of measuring the absolute composition of the air-nitrogen mixture inhaled, we used the Oximeter to indicate the degree of oxygenation of the blood. Table II gives data for two such tests. Fig. 4 is

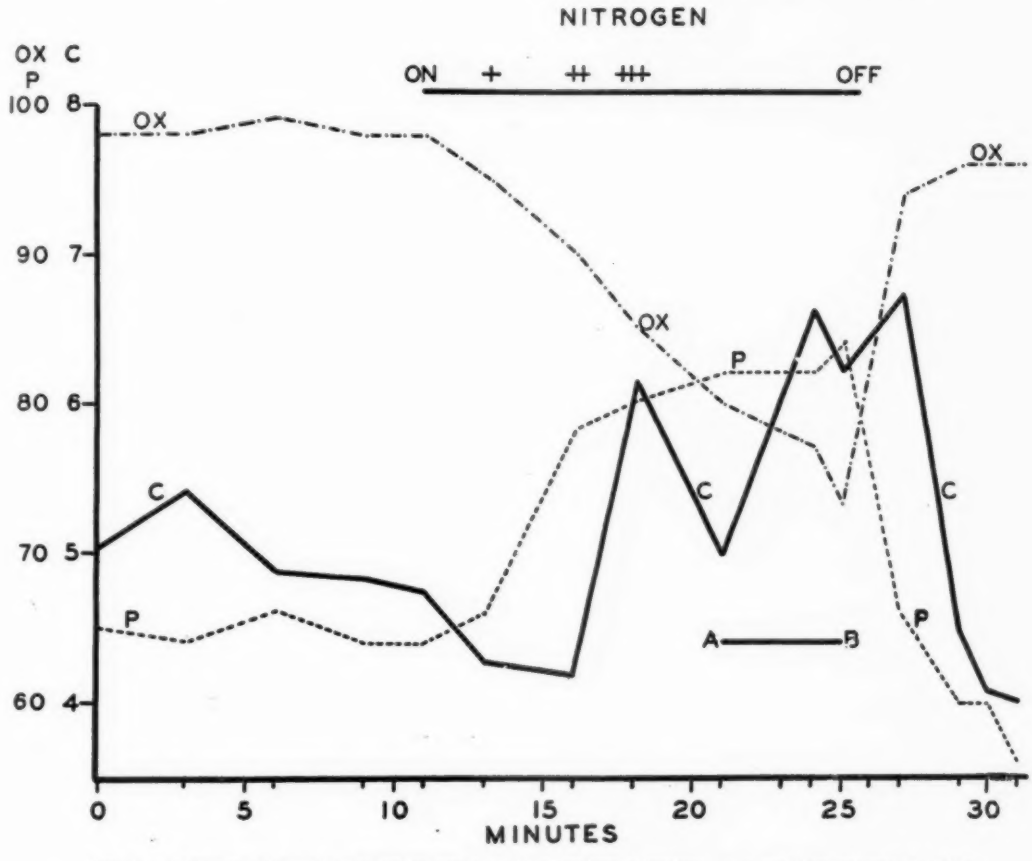

Fig. 4.—Influence of anoxia on cardiac output. Vertical coordinates: *C* = cardiac output, L./Min.; *Ox* = per cent oxygenation of blood; and *P* = pulse rate: beats per minute.
+, ++, +++ indicate increase in nitrogen content of inhaled nitrogen-air mixture.
A-B. Oximeter and pulse rate fluctuating widely with respiratory cycle.

a plot of the more drastic test (No. 2) in which oxygenation of the blood was reduced almost to 70 per cent. In this experiment, the heart sound meter data were read from the two microammeters already described. It is interesting that greater difficulty was found in counting pulse rate over thirty-second intervals than in reading the heart sound meter. In Experiment 2, between twenty and twenty-five minutes, the patient was breathing irregularly, the Oximeter galvanometer was making wide swings with inhalation and exhalation, and the pulse rate was so irregular that the rates recorded are probably lower than the pulse rates actually attained by the subject.

Grollman reports that in anoxia pulse rate rises before cardiac output and that output should increase when oxygenation of the blood falls to about 83 per cent. Our heart sound meter measurements show pulse rate to rise first, and cardiac output to rise definitely when the blood is about 85 per cent oxygenated.

Reduction of Cardiac Output by Exhaling Against Pressure.—A fall in cardiac output was produced by breathing for seven minutes against an exhalation pressure of 25 cm. of water. Table III shows the trend of cardiac output after the test.

The various procedures used to study measurement of cardiac output by the heart sound meter show that (1) under resting conditions it gives data comparable to that of the high-frequency ballistocardiograph, and (2) under conditions known to change cardiac output, but in which the ballistocardiograph may be unsuitable, the heart sound meter measurements conform in trend to those reported by observers using other methods.

The ease with which a single observer can make frequent measurements, merely reading the two microammeters of the heart sound meter and having few calculations to make, contrasts with the technical difficulties or tedious measurements of other methods and suggests that this new procedure may make possible many studies of cardiac output hitherto found impracticable.

TABLE III. INFLUENCE OF EXHALING AGAINST PRESSURE

	PULSE RATE	STROKE VOLUME C.C.	CARDIAC OUTPUT L./MIN.
Control 1			
Resting 10 min.	72	63	4.54
Control 2			
Resting 11 min.	71	63	4.47
Exhaling for 7 minutes against 25 cm. water			
20 seconds after test ended	79	37	2.92
90 seconds after test ended	84	56	4.54

SUMMARY

1. An electronic heart sound meter has been devised to convert the complex pattern of low-frequency cardiac vibrations picked up at the chest wall into a simple "resultant frequency."

2. The "resultant frequency" varies during each heart cycle in a manner similar to the ventricular volume curve.

3. Simultaneous records of the high-frequency ballistocardiograph and the heart sound meter made on rested, supine subjects show a close correlation between the cardiac output as calculated by Starr's formula,

$$11\sqrt{(I+J)C^{3/2}A}$$

and an "output" calculated from the formula,

$$S = f_1^2 - f_2^2$$

in which f_1 is the maximum "resultant frequency" occurring at commencement of systole, and f_2 is the minimum "resultant frequency" at the end of systole.

4. Records of the ballistocardiograph and the heart sound meter taken immediately after exercise do not give comparable calculations of cardiac output. However, heart sound meter data after moderate exercise, after anoxia produced by breathing nitrogen, and after the Flack Test show qualitative and quantitative trends comparable to data obtained by other procedures.

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RESPIRATORY MOVEMENT AS A FACTOR IN THE PRODUCTION OF Q WAVES IN LEAD I AND IN UNIPOLAR LEADS FROM THE LEFT PRECORDIUM IN HUMAN LEFT BUNDLE BRANCH BLOCK

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IN A recent article, Sodeman, Johnston, and Wilson[1] have emphasized the fact that a Q deflection seldom occurs in Lead I in human left bundle branch block. Goldberger[2] has also commented on this finding. In experimental canine left bundle branch block, on the other hand, a Q deflection frequently occurs in Lead I. This discrepancy could arise in one of two ways: (1) because of a difference in the order of excitation of the different parts of the ventricular muscle in human and in canine left bundle branch block, or (2) because of a difference in the disposition of the heart's surfaces with respect to the thoracic cage and the attachments of the limbs.

Precordial leads in both species, when left bundle branch block is present display such striking similarity in the configuration of the QRS complexes as to make it appear unlikely that there is any important difference in the order of ventricular excitation. This leaves the alternative suggestion of a difference in the position of the heart as the more probable explanation of the observed discrepancy. Some positive evidence may also be adduced in support of this explanation. For example, Foster,[4] in experiments referred to by Sodeman and co-workers, showed that in dogs in which the left branch of the bundle of His had been severed, a Q wave in Lead I could readily be produced by elevation of the apex, by displacement of the apex to the right, and by rotation of the heart in either direction on its longitudinal axis. When the same experiments were repeated on monkeys with left bundle branch block, the only maneuver by which a Q_1 could be produced was elevation of the apex to 45°, which resulted in a completely negative QS deflection in Lead I. From this and other evidence Sodeman and co-workers concluded that changes in position might readily lead to the production of a Q_1 in a vertically placed heart like the dog's, but were much less likely to do so in a more transversely lying heart like the monkey's or man's.

In further support of this contention, they looked for, but did not find, any peculiarities in the position of the heart in thirteen cases of human left bundle branch block showing a Q_1. In addition to their own thirteen cases, these au-

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*Clinical Fellow in Medicine of the American College of Physicians, 1946.

thors collected twenty-four others reported in the literature, making thirty-seven in all. Eight of these had come to autopsy. Six of the eight had had myocardial infarction, and in five of these six cases, gross lesions of the interventricular septum were present. Their final conclusion was that a Q wave in Lead I in human left bundle branch block, while not diagnostic, should arouse suspicion that a lesion of the ordinary muscle of the interventricular septum might be present, and they recommend that a full set of precordial leads be taken in such cases "not only for the purpose of ascertaining whether left bundle branch block is really present, but also to find out whether a Q deflection is present in leads from the left side of the precordium and left axilla."

With the septum intact, one would not expect Q deflections to occur in direct unipolar leads from the left ventricular surface in left bundle branch block. When this conduction defect is present the septum is activated entirely from right to left, and the left ventricular cavity is positive in the earliest stage of electrical activity. At this time the muscle of the free wall of the left ventricle has not yet been activated, and it transmits passively the positive cavity potentials to an overlying electrode. The first deflection recorded by the galvanometer must, therefore, be a positive one. Any extensive lesion of the septum, however, may modify these relationships. To quote Sodeman and his coworkers, "If the septum is extensively damaged, the electrical forces produced by its activities are reduced or abolished, and the initial negativity of the right ventricular cavity is transmitted to the left [cavity], and hence to those regions of the left side of the body that are initially positive in left bundle branch block when the septal muscle is healthy. When this happens, Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also . . . ."

REPORT OF A CASE

The following case is reported to show that under certain conditions a Q deflection may be caused to appear and disappear at will in human left bundle branch block, not only in Lead I but also in leads from the left precordium and the left axilla, merely by changes in the position of the heart induced by respiration.

The patient, J. C., was a man 66 years of age, who had been known to have essential hypertension for at least fifteen years. There had never been any chest pain, paroxysmal dyspnea, congestive failure, or other episode suggestive of myocardial infarction. The blood pressure in 1946 was 220/120. X-ray of the chest showed a cardiothoracic ratio of 13.5 to 28.5 and a fairly normal cardiac silhouette. A routine electrocardiogram showed left bundle branch block, and it was observed that not only did the amplitude of the deflections and the electrical axis in the standard limb leads undergo rhythmic variation with the respiratory cycle, but that, in addition, a Q wave appeared in Lead I in inspiration and disappeared in expiration.

To investigate the origin of these Q waves, a full set of unipolar precordial and extremity leads was taken in all phases of respiration. These curves are reproduced in Figs. 1 and 2. During expiration and midrespiration, all leads are entirely characteristic of classical left bundle branch block. The duration of the QRS is 0.14 second; Leads I, V_L, V_5, and V_6 all show a monophasic, double-peaked positive deflection with no Q waves. During inspiration, a pronounced and progressive change occurs, marked by a reduction in the amplitude of the bifid R waves and

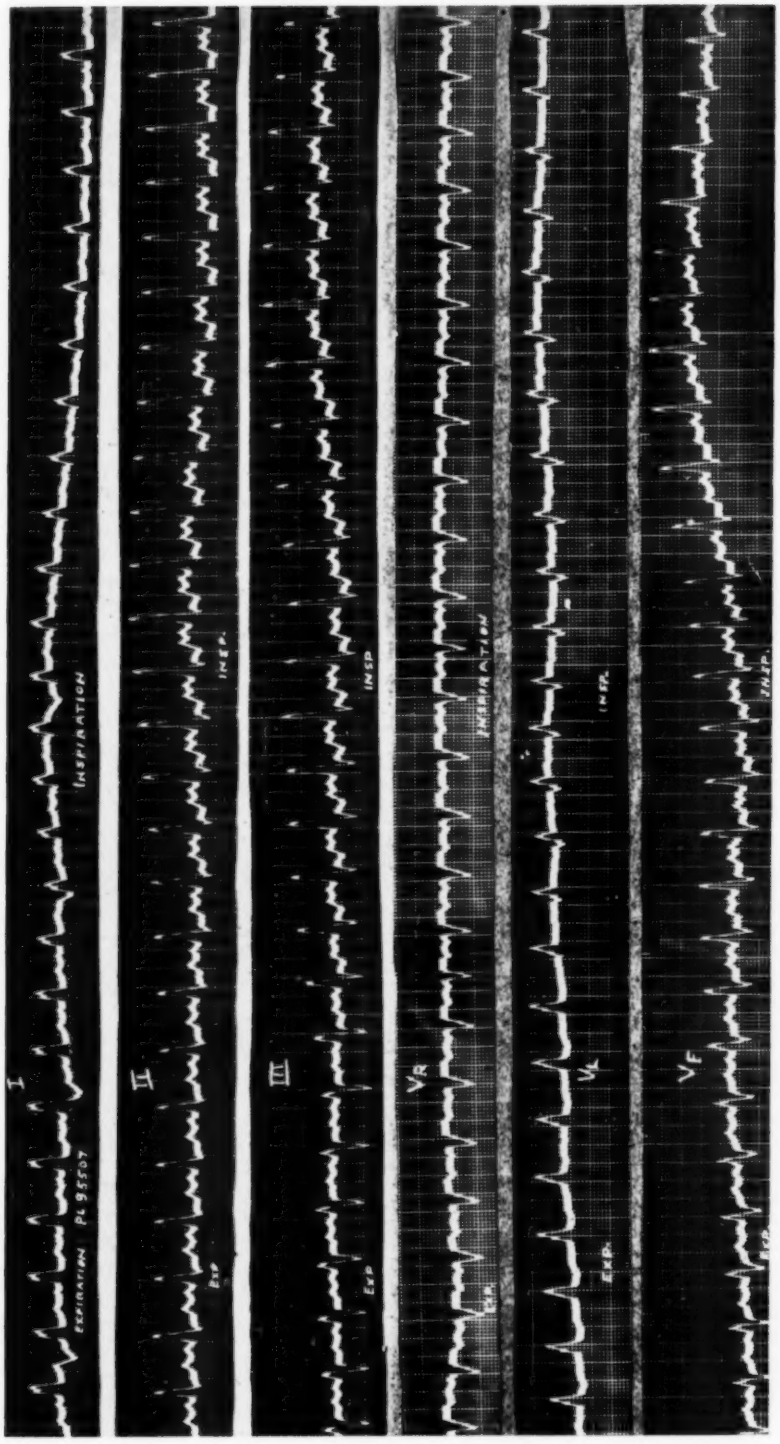

Fig. 1.—Note development of Q waves in Leads I and V_L with inspiration.

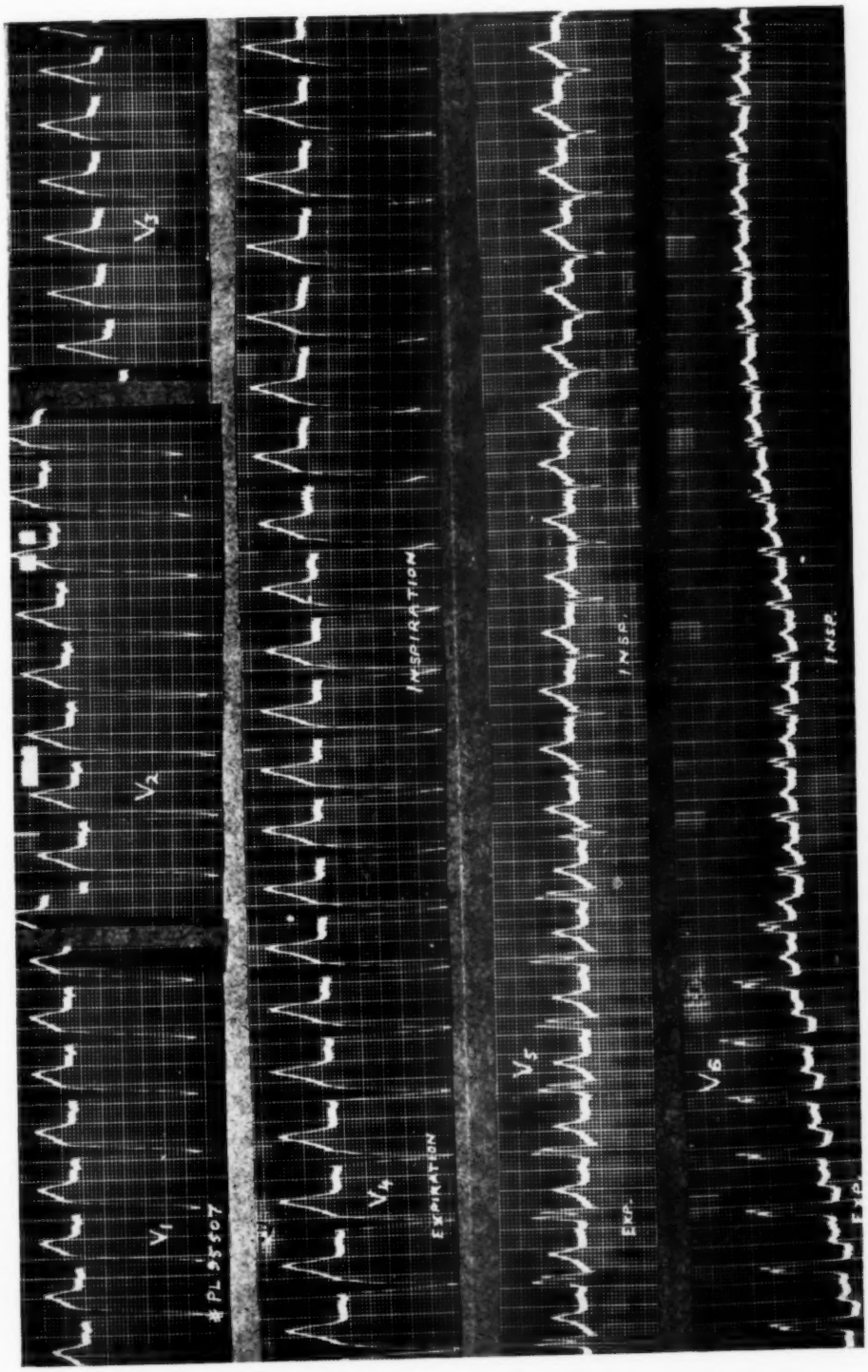

Fig. 2.—Note development of QS waves in Lead V5 and of Q wave in V6 with inspiration.

the development of a definite Q wave in Leads I, V_L, and V_6. In Lead V_5 a more extreme change occurs whereby the main QRS deflection, previously positive, becomes a completely negative QS deflection in deep inspiration. Leads V_R, V_1, V_2, and V_3 display little change; they consist of a deep QS deflection throughout the respiratory cycle. Lead V_4 shows a small R wave in expiration. With inspiration this becomes progressively smaller and ultimately disappears so that only a QS deflection remains. In Lead V_F the R wave becomes taller with inspiration and, as might be expected, a similar change occurs in Leads II and III.

DISCUSSION

The striking changes in QRS configuration shown in Figs. 1 and 2 may be considered under three headings: (a) Change in electrical axis; (b) development of Q waves over the left precordium; and (c) development of Q waves in Lead V_L and Lead I.

Change in Electrical Axis.—It is well known that the main electrical axis can be profoundly altered by changes in the position of the heart both when conduction is normal and when bundle branch block is present, and that such changes in position can be brought about by respiratory movements. The effect of deep inspiration is to cause the heart to assume a more vertical position and also to rotate clockwise on its longitudinal axis so as to bring the right ventricle in front of and above the left. This rotation produces modifications in the transmission to the limb attachments of the potential variations derived from the ventricular surfaces, so that the left ventricular potentials tend to be transmitted chiefly to the diaphragm and left leg, while the right ventricular potentials are transmitted to the left axilla. The effect on the electrical axis is a tendency to shift the axis toward the right. Expiration produces the opposite result; the heart assumes a more transverse position and, in addition, undergoes counterclockwise rotation on its longitudinal axis which tends to bring the left ventricle in front of and above the right, with transmission of left ventricular potentials to the left shoulder and right ventricular potentials to the diaphragm and leg. The electrical axis tends to shift to the left. Curves showing right axis deviation in human left bundle branch block associated with a vertical position of the heart have been published by Wilson and associates[3,6] and by Goldberger.[2,b] All these curves show a deep S wave in Lead I, but this is preceded in each case by a small R wave, so that no Q wave is present.

Q Deflections in Leads From the Left Precordium.—We have already reviewed the theoretical considerations that lead one to expect that in direct leads from the surface of the left ventricle in left bundle branch block the initial deflection will be positive. Precordial leads resemble the corresponding direct leads very closely as a general rule, but there are certain essential differences which should not be overlooked. A direct unipolar lead is taken from an electrode in actual contact with the epicardial surface; this electrode is influenced almost entirely by the potential variations of the muscle immediately underneath it, and only to a negligible extent by the potential variations of neighboring muscle. In such leads from the left ventricle in experimental uncomplicated left bundle branch block no Q wave has ever been recorded to our knowledge.

In precordial leads, on the other hand, the electrode is not in contact with the ventricular surface, but is separated from it by a considerable layer of tissue that varies with the thickness of the chest wall. Accordingly, these leads do not necessarily record in pure form the potential variations of a limited epicardial area. Wilson and co-workers[3] have expressed this relationship as follows: "The potential variations of every element of the epicardial surface contribute in some measure to the potential variations of an electrode placed upon the precordium. But, the magnitude of the contribution made by the potential variations of any given surface element is large if its distance from the electrode is small, and vice versa; it varies roughly as the inverse cube of this distance. For this reason, the potential variations of a precordial electrode are determined to a very large extent by the potential variations of the elements of ventricular surface nearest it. If all or the great majority of these elements simultaneously display potential variations of the same sort, the potential variations of the electrode are of the same character, through much smaller. If, on the other hand, the various elements that are more or less equidistant from the electrode display potential variations of different kinds, the potential variations of the electrode represent a mixture which may not resemble any of its components very closely."

The conditions last described may be produced when an electrode is placed on the precordium over the transitional zone between right and left ventricles. Such an electrode registers a mixture of potentials in which either right or left ventricular influence may predominate as the electrode is moved even slightly toward one side or the other; the same effect is produced if the electrode remains stationary while the heart undergoes rotation, so that the septum moves to right or left of the electrode. In left bundle branch block the complexes derived from right and left ventricles are so distinctive in configuration that even when partially fused, the components contributed by each ventricle remain clearly recognizable.

Fusion of this sort can be seen to occur in Lead V_5 (Fig. 2). During expiration it records in pure form the broad, double-peaked monophasic complex characteristic of leads from the left ventricle in left bundle branch block; there is no Q wave. With the beginning of inspiration the heart is rotated in clockwise fashion on its longitudinal axis, so that the front of the interventricular septum swings to the left. This brings the transition zone closer to the V_5 electrode, and the left ventricular pattern begins to be modified by potentials derived from the right ventricle. The first noticeable effect is the appearance of a tiny notch on the upstroke of the initial R wave. This notch probably represents the small R wave which is present in Lead V_4 in expiration but which disappears in inspiration. As the transition zone swings farther leftward, the potentials derived from the right ventricle begin to dominate those derived from the left: the double positive peaks of the original V_5 complex become lower and lower until finally they appear as mere notches on the descending and ascending limbs of a deep QS deflection representing negative potentials derived from the right ventricle.

Fig. 3 represents a simultaneous recording of Leads V_4 and V_5 at triple camera speed (in expiration, *A*; early inspiration, *B*; and slightly deeper inspiration, *C*) to demonstrate more clearly the time relationships of the various deflections in the two leads. It will be seen that a Q wave in Lead V_5 does not appear in Fig. 3,*A* or *B*, but only in *C* after the R wave in Lead V_4 has disappeared. Unfortunately, no simultaneous record was obtained in really deep inspiration, but the manner of development of the deep negative deflection in Lead V_5 seen toward the right of Fig. 2 is already clearly indicated.

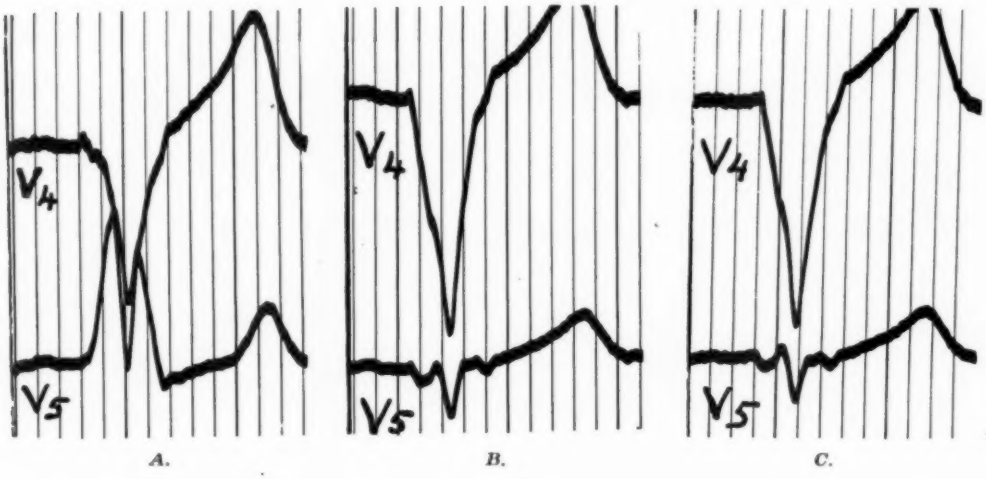

Fig. 3.—Simultaneous recording of Leads V_4 and V_5 (triple camera speed). *A*, expiration; *B* beginning inspiration; *C*, somewhat deeper inspiration. Note disappearance of R in V_4 and coincident appearance of Q in V_5 in *C*.

The changes described in Lead V_5 may be seen in modified form in Lead V_6. Since this electrode is farther from the transition zone than in Lead V_5, the influence of the right ventricle is less pronounced; but in deep inspiration it is sufficient to produce a marked reduction in the amplitude of the R waves and the appearance of a definite Q wave, the origin of which is undoubtedly the same as that of the deeper QS deflection in Lead V_5.

In order for a Q wave to occur in leads from the left precordium in left bundle branch block as a result of fusion effects such as we have postulated, certain special conditions must be met. Of these, the most important is that there must be no R waves in leads from the right precordium. In the present case it is true that Lead V_4 did show a tiny R wave, but with inspiration and shift of the septum leftward it rapidly disappeared. It is noteworthy in this connection that left bundle branch block occurs most frequently in hypertensive and arteriosclerotic hearts in which the left ventricle is hypertrophied, a condition which, by itself, may cause suppression of R waves over the right precordium.

Q Deflections in Lead I and Lead V_L.—Lead I is a record of the difference in potential from moment to moment at the attachments of the arms: Lead I = Lead V_L – Lead V_R. It will be seen in Fig. 1 that V_R showed little or no variation with respiration, maintaining a QS configuration throughout, and, accordingly, any changes occurring in Lead I must be attributed chiefly to potential variations at the left shoulder. Both Lead I and Lead V_L developed a conspicuous Q wave in inspiration. It is entirely likely that the origin of this deflection is the same as that of the Q waves in Leads V_5 and V_6, that is, from potentials transmitted from the right ventricle as the heart rotates with inspiration.

There is, however, another possible explanation for the presence of these Q waves. During inspiration the heart assumes a more vertical position in the thorax and becomes more symmetrically disposed with respect to the two shoulders, so that the left shoulder as well as the right may come to face part of the auricles, great vessels, and valvular orifices at the base of the heart. Its potentials will then represent a mixture of those from the ventricular cavities and those from the lateral aspect of the ventricles. During forced inspiration there may be sufficient clockwise rotation on the heart's long axis to bring the right side of the interventricular septum opposite the left shoulder, in which case activation of the septum from right to left would give rise to initial negativity at the left shoulder. During expiration, the heart resumes its more transverse position and the left shoulder no longer faces into the cavities. Its potentials are now derived chiefly from the lateral aspect of the ventricular surface and are represented by the familiar broad, bifid, positive complexes.

It is probable that the explanation for the common occurrence of a Q_1 in canine left bundle branch lies along these lines. In the dog the heart occupies a very vertical position. Curves published by Wilson and co-workers[3] show that when conduction is normal the ventricular complexes in Leads V_R and V_L are very similar, both consisting chiefly of a deep negative deflection, which indicates that both forelimb attachments face the ventricular orifices. In curves from canine left bundle branch block shown in the same article there is a definite Q wave in Lead I, although none appears in leads from the left precordium. These curves show well-marked R waves in leads from the C_1, C_2, C_3, and C_4 positions, so that even at the transition zone there can be no opportunity for the development of Q waves by fusion of complexes derived from right and left ventricles in the manner suggested.

SUMMARY

1. Electrocardiograms are presented which show transient Q waves in Leads I, V_L, V_5, and V_6 in association with left bundle branch block. These Q waves appear and disappear during the respiratory cycle. There is nothing in the patient's history or examination to suggest that he had ever had a myocardial infarct.

2. It is suggested that the Q waves over the left precordium may be produced by fusion of right and left ventricular complexes as the interventricular

septum swings toward the left during inspiration, and that the Q waves in Leads I and V_L probably arise on the same basis. Special conditions that must be present for this to occur are indicated.

3. An alternative explanation is offered with respect to the origin of Q waves in Lead V_L and Lead I, based on the assumption of an unusually vertical position of the heart during inspiration. It is suggested that the more vertical position of the dog's heart is responsible for the frequent occurrence of Q_1 in canine left bundle branch block.

The authors wish to acknowledge the kindness of Dr. Frank N. Wilson in reviewing the manuscript of this paper.

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ELECTROKYMOGRAPHIC STUDIES OF ASYNCHRONISM OF EJECTION FROM THE VENTRICLES

Normal Subjects and Patients With Bundle Branch Block

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THE development of the electrokymograph[1-3] provides a new method for studying the motions of the borders of the heart and great vessels in man. With this instrument, records can be obtained of the movements of these borders which accompany ejection of blood from the ventricles. The time relationships of the events recorded from the pulmonary artery and the right ventricle can be compared with those from the ascending aorta and left ventricle. Thus, synchronism or asynchronism of the ejection phases of the two sides of the heart can be determined.

Earlier studies, utilizing the myocardiograph[4,5] or solenoid recorder,[6] indicated that contraction of the ventricles could be asynchronous in normal animals. Asynchronism was also demonstrated after cutting a branch of the bundle of His. Katz,[7] in 1925, recorded intraventricular and intra-arterial pressures in normal dogs and conclusively showed that ejection of blood from the ventricles was not simultaneous in most instances.

The principal methods of studying this problem which have been applied to man include the analysis of (1) the carotid sphygmogram with simultaneously recorded standard lead electrocardiogram, (2) the roentgenkymogram of the pulmonary artery and ascending aorta, (3) the roentgenkymogram with electrocardiogram, (4) the stethogram, carotid sphygmogram, and electrocardiogram, and (5) the right and left "part-electrocardiogram" and stethogram.[8-12] Despite questions raised as to the reliability of some of these methods for accurately timing cardiovascular phenomena, results generally indicated that asynchronism of ejection occurred, commonly in normal subjects and usually in patients with electrocardiographic evidence of bundle branch block.

This paper is a report on the application of the electrokymograph to the study of ventricular asynchronism.

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METHOD

The motion of the border of the pulmonary artery segment of the cardiovascular silhouette and that of the ascending aorta close to its point of origin were recorded consecutively. These electrokymograms (E.K.Y.) closely resemble the carotid sphygmogram which was recorded simultaneously with each. The time interval from the onset of ejection on the pulmonary artery electrokymogram to the onset of ejection on the carotid sphygmogram was measured and was designated PAc. In the same way, the time interval from the onset of ejection

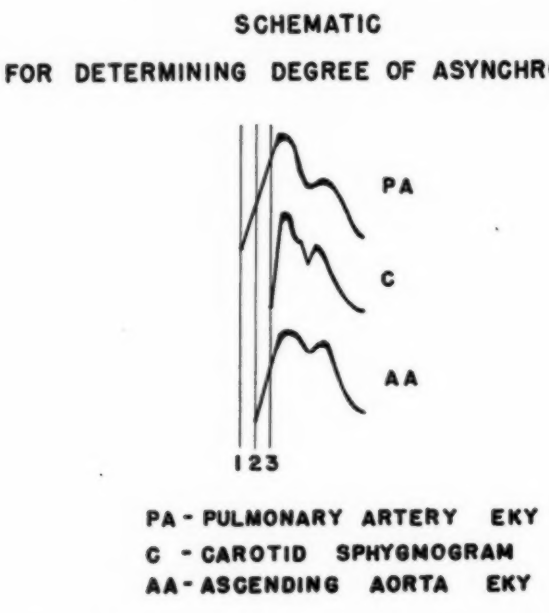

Fig. 1.—Diagrammatic sketch illustrating principles of method. Vertical time lines *1, 2, 3* mark onset of ejection wave on pulmonary artery (*PA*), ascending aorta (*AA*), and carotid artery (*C*), respectively.

1 to *3* = PAc

2 to *3* = AAc

1 to *2* = PAc to AAc difference, a measure of relative time of ejection into these two vessels.

In practice, the records of pulmonary and ascending aorta motion are separately recorded (Fig. 2) in each case simultaneously with the carotid sphygmogram.

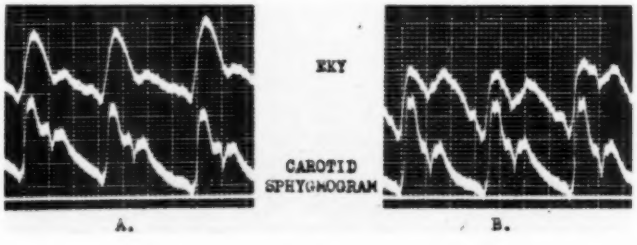

Fig. 2.—Normal electrokymograms representing motion of borders of pulmonary artery (*A*) and ascending aorta (*B*). Lower tracing in each case is carotid sphygmogram. Time and amplitude markings same as in electrocardiogram. PAc = 0.02 second and AAc = 0.02 second, indicating simultaneous ejection of blood from ventricles.

on the ascending aorta electrokymogram to the onset of ejection on the carotid sphygmogram was measured and was designated AAc. The carotid sphygmogram thus served as a common point of reference for determining the time interval between the onset of ejection on the pulmonary artery and the ascending aorta electrokymograms (Figs. 1 and 2). For example, in Fig. 2 the time difference between ejection on the pulmonary artery and the carotid artery curves was 0.02 second, and the ascending aorta to carotid time difference was 0.02 second. When, as in this case, PAc and AAc are equal, the interpretation was that these vessels received blood simultaneously and both ventricles ejected blood simultaneously (Table I, Subjects 22 through 35). When the pulmonary artery to

TABLE I. DATA ON NORMAL VENTRICULAR ASYNCHRONISM (SIXTY-EIGHT ADULTS, 17 TO 32 YEARS OF AGE, WITHOUT CARDIOVASCULAR DISEASE)

PATIENT NO.	PAc	AAc	PAc TO AAc DIFFERENCE*	LEADING VENTRICLE	PATIENT NO.	PAc	AAc	PAc TO AAc DIFFERENCE*	LEADING VENTRICLE
1	.03	.00	.03	Right	35	.01	.01	.00	Even
2	.03	.00	.03	Right	36	.00	.01	−.01	Left
3	.03	.01	.02	Right	37	.02	.03	−.01	Left
4	.03	.01	.02	Right	38	.01	.02	−.01	Left
5	.03	.01	.02	Right	39	.01	.02	−.01	Left
6	.03	.01	.02	Right	40	.01	.02	−.01	Left
7	.03	.01	.02	Right	41	.00	.01	−.01	Left
8	.03	.01	.02	Right	42	.00	.01	−.01	Left
9	.01	.00	.01	Right	43	.01	.02	−.01	Left
10	.02	.01	.01	Right	44	.00	.01	−.01	Left
11	.01	.00	.01	Right	45	.02	.03	−.01	Left
12	.01	.00	.01	Right	46	−.01	.00	−.01	Left
13	.03	.02	.01	Right	47	.00	.01	−.01	Left
14	.01	.00	.01	Right	48	.01	.02	−.01	Left
15	.03	.02	.01	Right	49	.00	.01	−.01	Left
16	.02	.01	.01	Right	50	.02	.03	−.01	Left
17	.02	.01	.01	Right	51	.00	.01	−.01	Left
18	.02	.01	.01	Right	52	.01	.02	−.01	Left
19	.02	.01	.01	Right	53	.01	.02	−.01	Left
20	.02	.01	.01	Right	54	.01	.02	−.01	Left
21	.03	.02	.01	Right	55	−.01	.01	−.02	Left
22	.01	.01	.00	Even	56	.01	.03	−.02	Left
23	.01	.01	.00	Even	57	−.01	.01	−.02	Left
24	.02	.02	.00	Even	58	−.01	.01	−.02	Left
25	.01	.01	.00	Even	59	−.01	.01	−.02	Left
26	.01	.01	.00	Even	60	−.01	.01	−.02	Left
27	.03	.03	.00	Even	61	−.01	.01	−.02	Left
28	.02	.02	.00	Even	62	−.01	.01	−.02	Left
29	.01	.01	.00	Even	63	−.01	.01	−.02	Left
30	.00	.00	.00	Even	64	.00	.02	−.02	Left
31	.03	.03	.00	Even−	65	−.01	.01	−.02	Left
32	.00	.00	.00	Even	66	−.01	.02	−.03	Left
33	.02	.02	.00	Even	67	−.01	.02	−.03	Left
34	.02	.02	.00	Even	68	−.01	.02	−.03	Left

PAc = Interval from ejection on pulmonary artery E.K.Y. to ejection on carotid sphygmogram. Plus value means pulmonary artery ejection precedes carotid ejection. Minus (−) value means pulmonary artery ejection follows carotid ejection.

AAC = Interval from ejection on ascending aorta E.K.Y. to ejection on carotid sphygmogram. All times in seconds.

*Plus value means pulmonary artery ejection precedes ascending aorta ejection. Minus (−) value means pulmonary artery ejection follows ascending aorta ejection.

carotid time (PAc) was longer than the ascending aorta to carotid time (AAc) the interpretation was that the right ventricle ejected its blood first (Subjects 1 through 21). When AAc was longer than PAc the interpretation was that the left ventricle ejected its blood first (Subjects 36 through 68).

Wolferth and Margolies[8] and Hirsch and Gubner[9] used the roentgenkymograms of aortic and pulmonary arterial waves for studying asynchronism in the ejection phases of the two ventricles. The method proposed herein differs only in the manner in which the records are obtained and timing is determined.

The electrokymogram is an electrical and instantaneous recording, while the carotid sphygmogram is recorded by an air conduction system. We have measured the lag in this latter system and it is consistently 0.01 second for the six feet of tubing we utilize. This correction factor was applied to all the time measurements.

The use of the carotid sphygmogram as a common time-reference curve is considered valid as long as no significant cardiodynamic changes occur between the time the ascending aorta and pulmonary artery records are obtained. The great vessel records were taken within two or three minutes of one another with the patient standing in a relaxed position. Preliminary observations indicated that the time relationships between the onset of ejection on the pulmonary artery, ascending aorta, and carotid curves do not vary significantly under these conditions. Measurements were the same whether right or left carotid sphygmograms were used.

The records are obtained at comparable points on the ascending aorta and pulmonary artery close to the respective semilunar valves. Some variations will occur in selecting the points of recording. The errors introduced by this and by differences in pulse wave transmission times in the two vessels are less than the 0.01 second error inherent in the method and, therefore, insignificant.

The sixty-eight normal subjects were medical students and nurses, 17 to 32 years of age, with no evidence of cardiovascular disease. The sixteen subjects with intraventricular block had standard and precordial electrocardiograms taken. In all cases, two qualified examiners agreed as to the electrocardiographic diagnosis.

RESULTS

In Normal Subjects.—Table I shows the results of measurements of asynchronism in the normal adults studied. Asynchronism of ejection occurred in fifty-four of sixty-eight subjects. Left ventricular ejection led by 0.01 to 0.03 second in thirty-three cases; right ventricular ejection led by 0.01 to 0.03 second in twenty-one cases; and ejection appeared synchronous in fourteen cases. These results are strikingly similar to those obtained by Katz[7] in his work with dogs, both as to the degree of asynchronism and as to the order of ventricular ejection.

These measurements were obtained on young adults. In older subjects, more rapid transmission of the pulse wave might be expected, possibly altering measurements and relationships. However, in a small group of older adults no significant variations were noted in the PAc and AAc measurements.

It is of interest to note in Table I that the PAc interval normally varies within a narrow range (+0.03 to −0.01 second). Ejection on the pulmonary artery may follow that on the carotid artery (PAc = −0.01 second) when the left ventricle ejects its blood sufficiently in advance of the right ventricle.[13] It should be noted also that the PAc interval alone does not measure the exact degree of ventricular asynchronism or indicate which ventricle ejects its blood first. To determine this from the PAc measurement, it would be necessary to take into account (1) the difference in speed of pulse wave transmission, and (2) the difference in distance from the ventricles to the points of recording on the pulmonary and carotid arteries.

Measurements of ascending aorta to carotid transmission time varied from 0.00 to 0.03 second. A transmission time of 0.01 to 0.02 second closely agrees with previous estimates, but times of 0.03 and particularly of 0.00 would seem erroneous. There are two possible explanations for this: (1) The measurements are probably accurate only to within 0.01 second, and (2) it is known that positional changes can occur on the ascending aorta during isometric contraction of the ventricles. If this positional change results in lateral motion of the vessel border, it will occur just prior to and may merge with the lateral movement as a result of ejection of blood. What appeared to be the onset of the ejection wave might actually be the onset of the positional change and thus give an apparently prolonged AAc time. If, on the other hand, the positional change results in medial motion of the vessel border, it may offset the beginning of lateral motion resulting from ejection and delay the upstroke of the ejection wave. In most cases, it is possible to distinguish these positional changes when they occur. More detailed study of the pulse wave transmission times as measured by the electrokymograph will be the subject of a separate report.

In view of these sources of error, it is probable that when readings of 0.00 and 0.03 second were obtained, the true values were closer to 0.01 and 0.02 second, respectively. When the PAc to AAc difference was recalculated after these latter values were arbitrarily assumed for the AAc time, the findings differed very little from those of Table I. The number of subjects showing the left ventricle leading became thirty-two (thirty-three in Table I); cases showing synchronous ejection became seventeen (fourteen in Table I); cases showing the right ventricle in the lead became nineteen (twenty-one in Table I).

In Patients With Intraventricular Block.—The same method of study was applied to a group of sixteen patients with clear-cut electrocardiographic signs of left or right bundle branch block. (No cases of unclassified or indeterminate block were encountered.) It was immediately apparent that the PAc time was significantly altered as compared with that of the normal subjects. In 100 normal young adults, ejection on the pulmonary artery occurred from 0.03 second before to 0.01 second after ejection on the carotid artery (that is, PAc = 0.03 to −0.01 second). As shown in Table II, in fifteen of our subjects with bundle branch block, this PAc measurement fell outside the normal range. It measured more than 0.03 second in nine of ten patients with left bundle branch block and less than −0.01 second in each of six patients with right bundle branch block

(examples shown in Figs. 3, 4, and 5). These findings suggested that the measurement of the PAc interval alone might be adequate to detect bundle branch block. Before this was accepted as a valid single criterion, other possible criteria were studied.

TABLE II. RESULTS OF ASYNCHRONISM STUDIES IN BUNDLE BRANCH BLOCK

DIAGNOSIS BY ECG	PAc IN SECONDS	INTERPRETATION*
Right bundle branch block		
W. F.	−.05	Definite bundle branch block
E. H.	−.05	Definite bundle branch block
W. K.	−.05	Definite bundle branch block
L. M.	−.05	Definite bundle branch block
E. M.	−.04	Definite bundle branch block
B. Y.	−.04	Definite bundle branch block
Left bundle branch block		
W. C.	+.07	Definite bundle branch block
J. K.	+.07	Definite bundle branch block
H. S.	+.07	Definite bundle branch block
M. H.	+.07	Definite bundle branch block
B. L.	+.06	Definite bundle branch block
J. Z.	+.06	Definite bundle branch block
Be. L.	+.05	Definite bundle branch block
H. A.	+.04	Borderline bundle branch block
R. M.	+.04	Borderline bundle branch block
C. J.	+.03	Normal

*Note: "Normal" = PAc + 0.03 to −0.01 second; "borderline" = PAc within 0.01 second of "normal"; "definite" = PAc more than 0.01 second outside "normal."

At the time these patients were examined, both the electrokymograph and the technique of its use were in a developmental stage and we obtained satisfactory records of the motions of the ascending aorta in only five of the sixteen patients. In them it was possible to determine the degree of ventricular asynchronism by comparing PAc and AAc measurements, as was done with the normal subjects. These five were individuals with left bundle branch block. Their PAc to AAc difference measured 0.07, 0.06, 0.05, 0.04, and 0.03 second, respectively (upper limit of normal, 0.03 second). Thus, in all but one case, the degree of ventricular asynchronism was abnormally increased and the lag in left ventricular ejection was greater than in normal subjects. The same conclusion was reached from analysis of the PAc measurement alone in all but one patient (B. L.). In this patient, the PAc measurement (0.06 second) indicated a distinct left bundle branch block, while the PAc to AAc difference gave a reading of 0.03 second, which is within the normal variation.

There were twelve among the group of sixteen patients with intraventricular block in whom we failed to obtain satisfactory records of the ascending aorta but had good electrokymograms of the aortic knob. This information was used to calculate the time of ejection into the ascending aorta. The time for transmission of the pulse wave from the ascending aorta to the aortic knob was found to average 0.014 second (0.00 to 0.03 second) by electrokymographic

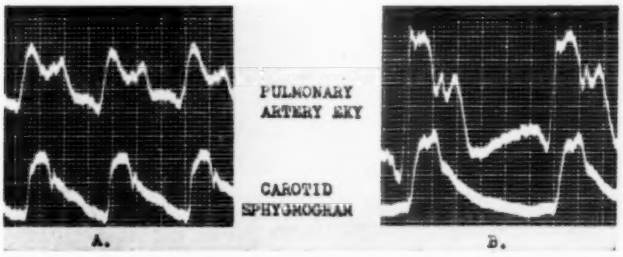

Fig. 3.—Electrokymogram illustrating left bundle branch block. *A*, B. L., 52 years of age, man. Electrocardiogram shows left bundle branch block (QRS, 0.14 second), PAc = 0.07 second. *B*, H. S., 39 years of age, man. Electrocardiogram shows left bundle branch block with A-V dissociation (QRS, 0.14 second), PAc = 0.08 second.

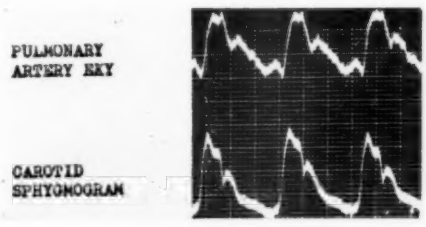

Fig. 4.—Electrokymogram illustrating right bundle branch block. E. M., 42-year-old man. Electrocardiogram shows right bundle branch block (QRS, 0.14 second). PAc = −0.03 second.

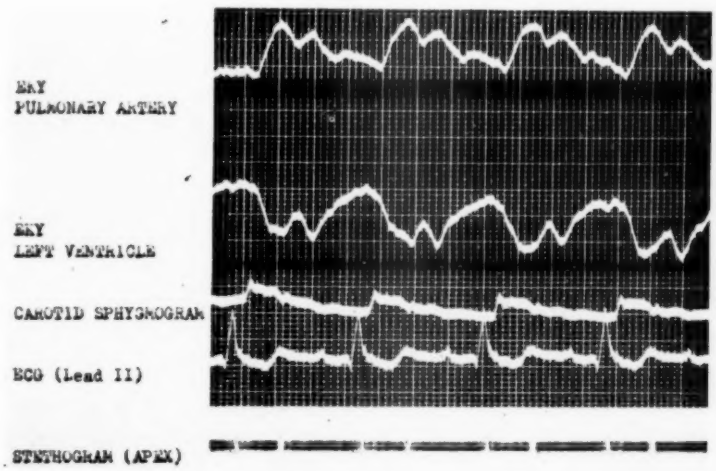

Fig. 5.—Example of right bundle branch block and simultaneous recording of multiple events. Lead II of electrocardiogram shown. Standard and precordial leads show right bundle branch block (QRS, 0.15 second), PAc = −0.05 second.

study. By applying this correction factor to the AKc time (ejection on the aortic knob electrokymogram to ejection on the carotid syphgmogram), we obtained an estimated AAc interval for each of these twelve cases. With this method, the PAc to AAc difference was outside normal limits, varying from 0.04 to 0.07 second, in eleven patients; while in one, B. L., it measured 0.03 second, the upper limit of normal. Wolferth and associates[13] compared the onset of ejection on the aortic knob and pulmonary artery segments of the roentgenkymograms of patients with left bundle branch block. By allowing 0.01 second for transmission from the ascending aorta to the aortic knob, they were able to calculate the difference between the time of ejection on the ascending aorta and pulmonary artery. This difference varied from 0.04 to 0.07 second in patients with left bundle branch block, agreeing with our results.

All these cross correlations of the PAc, AAc, and AKc times gave results in excellent agreement with those we obtained from analyzing the PAc time alone. It appears, therefore, that the simpler determination of the pulmonary artery to carotid time alone will detect abnormal degrees of ventricular asynchronism.

COMMENTS

The results obtained by these studies of normal man closely correspond with those found by Katz[7] in his study of dogs. In twenty-four experiments he found that right ventricular ejection preceded in eleven instances by 0.016 to 0.027 second; left ventricular ejection preceded in eleven instances by 0.013 to 0.03 second; ejection from the two ventricles was simultaneous in two cases. In both his and our studies, asynchronous ejection occurred more commonly than synchronous ejection: either the right or left ventricle led in about the same percentage of cases. Our findings were also in accord with those of Katz in regard to the degree of asynchronism observed.

With the electrokymograph the motion of the right and left ventricular borders can be recorded. The most direct method for studying contraction and ejection phenomena would be to record these simultaneously and make a direct comparison of activities. However, the technique of simultaneously recording motion of the two ventricles is difficult and requires special apparatus. The records obtained so far have not shown sharply defined and measurable points of ejection.

Another approach is to record simultaneously electrokymograms of the pulmonary artery and the ascending aorta. We have not been able to do this in a group of normal young people because the anatomic position of these two vessels was such that they could not both be brought into silhouette at the same time. In one of three attempts with older individuals with bundle branch block, we obtained satisfactory simultaneous recordings of these two great vessels. This record indicated a left bundle branch block of the same degree as found by analysis of the single electrokymogram of the pulmonary artery and the carotid sphygmogram.

It is simpler and quicker to analyze the pulmonary artery electrokymogram than to use the more complex methods. The measurement of the PAc interval alone appears adequate for detecting increased degrees of asynchronism in patients with intraventricular block.

SUMMARY

1. The electrokymograph was utilized to study asynchronism of ejection from the ventricles of man.

2. Analysis of electrokymograms from the pulmonary artery and the ascending aorta demonstrated that asynchronous ventricular ejection was more frequent than synchronous ejection in the normal subjects studied.

3. A simple method of detecting increased degrees of asynchronism in patients with bundle branch block was demonstrated, utilizing the pulmonary artery electrokymograms and the simultaneously recorded carotid sphygmogram.

4. In patients with left bundle branch block, the ejection wave on the pulmonary artery curve preceded that on the carotid record by a significantly greater time than in the normal subjects.

5. In patients with right bundle branch block, the ejection wave on the pulmonary artery curve occurred after that on the carotid record by a significantly greater time than in the normal subjects.

Electrocardiograms were interpreted by Doctor Hugo Roesler, who gave invaluable encouragement and aid in this study.

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ON THE EVIDENCE FOR GENERALIZED ARTERIOLAR CONSTRICTION IN COARCTATION OF THE AORTA

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IN 1938, Steele and Cohn,[1] and in 1941, Steele[2] advanced the opinion that the hypertension which is present in the arms in most cases of coarctation of the aorta is not solely due to the direct mechanical effects of the lesion, but rather that it is due to the occurrence of increased arteriolar tone throughout the body. The significance of experiments with acute obstruction of the aorta performed by Brotchner,[3] which he interpreted as supporting the opinion expressed earlier by Blumgart, Lawrence, and Ernstene[4] (who believed that the hypertension is of purely mechanical causation), has been discounted by Steele.[2]

The opinion that widespread arteriolar constriction exists is based on two pieces of evidence. The first is the finding of Prinzmetal and Wilson[5] and of Pickering,[6] who independently noted that in cases of coarctation the resting volume of blood flow through the hand and forearm, as estimated by a plethysmographic method, was not increased above the normal. This finding is interpreted as evidence for the existence of arteriolar constriction in the upper portion of the body. The second is the observation of Steele and Cohn,[1] and of Steele,[2] that in two of three cases of coarctation of the aorta, diastolic pressure in the femoral artery, measured directly, was increased above normal levels. This observation was interpreted by Steele[2] as evidence of general increase in arteriolar tone throughout the body.

The observations of Prinzmetal and Wilson and those of Pickering do not, however, afford positive proof of the existence of arteriolar constriction in the upper portion of the body in coarctation of the aorta; a body of purely clinical evidence suggests strongly that, at least in some cases, blood flow is increased through tissues supplied by arteries which take origin above the constricted isthmus, and decreased in the regions supplied by arteries which arise below the obstruction. In this body of evidence, which has recently been summarized by Reifenstein and associates,[7] may be mentioned warm hands and cold feet, high facial coloring,[8] numbness and pallor of the feet and legs, overdevelopment of the upper as compared with the lower extremities, and intermittent claudication.[4] The occurrence of a capillary pulse in the lips[8] is also strong but not incontrovertible evidence against the existence of arteriolar constriction in this region.

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It should be noted, also, that if *uniform* arteriolar constriction throughout the body exists in coarctation of the aorta, the flow of blood through the upper portion of the body should be increased and that through the lower portion decreased, just the same as if arteriolar tone throughout the body were normal. If flow is not increased in the tissues which receive blood from the aorta above the constricted isthmus, it must follow that flow in the tissues which receive blood from arteries which arise below the isthmus is not decreased, and therefore, that *selective* constriction of the arterioles in the upper portion of the body exists.

With regard to the significance of the second piece of evidence, elevation of the diastolic pressure in the femoral artery cannot, per se, be interpreted as evidence for a general increase in arteriolar tone throughout the body. The pressure in a given peripheral artery furnishes an accurate index of peripheral resistance throughout the body (in relation to cardiac output and the capacity of the arterial tree) only if no abnormal resistance intervenes between the heart and this artery to oppose the flow of blood or to interfere with the transmission of pressure waves.

Further, the cardiac output, the capacity of the arterial system, and the magnitude of the factors which oppose the flow of blood determine *mean* pressure in the aorta; no one of them determines the level of diastolic pressure. Systolic pressure, diastolic pressure, and all other instantaneous pressures depend upon the mean pressure and upon the amplitude and form of the aortic pressure pulse. Obviously, if the pulse is of large amplitude, the values for systolic, mean, and diastolic pressure are widely separated, while if the amplitude of the pulse is small, these values all lie close together. Thus, it is quite possible, if the pressure pulse is of abnormally small amplitude, for the diastolic pressure to be elevated even though mean pressure is decreased. Normally, mean intra-aortic pressure is about 105 mm. Hg; systolic pressure, 130; diastolic, 85; and pulse pressure, 45. Should factors intervene to reduce mean pressure to 98 and pulse pressure to 10, systolic pressure might then be 103, and diastolic, 93.

In coarctation of the aorta, an abnormal resistance to the flow of blood and to the transmission of pressure waves is interposed between the upper and lower segments of the aorta. For reasons that are quite clear, this resistance causes elevation of mean pressure in the proximal segment and increase in the amplitude of its pressure pulse. These changes are reflected in the pressures in the brachial artery. For the same reasons, mean pressure in the distal portion is lower than that in the proximal segment, and the pressure pulse in the distal aorta is markedly decreased in amplitude. These changes are reflected in the pressures in the femoral artery.

In the brachial artery, diastolic pressure is considerably removed from mean pressure, while in the femoral artery diastolic pressure is much nearer the mean. For this reason, it should be expected that diastolic pressure in the femoral artery might well be as high as or higher than diastolic pressure in the brachial

artery; this is especially likely to be the case if mean pressure in the distal aorta is not greatly below that in the proximal segment.

Other examples of elevation of the diastolic pressure as a result solely of decrease in the amplitude of the pulse wave may be cited.

1. In instances of partial obstruction of one subclavian artery by pressure of an aortic aneurysm or due to sclerotic change, diastolic pressure in the brachial artery of the obstructed side is often higher than that in the opposite arm. In a patient recently seen by the writer, there was partial obstruction of the right subclavian artery. The pulse at the left wrist was of normal volume; that at the right, very small. Arterial pressure in the left arm was 140/90; in the right, 115/105. The elevation of diastolic pressure is due to marked decrease in the amplitude of the pulse wave associated with only slight reduction in the mean pressure.

2. In normal subjects, application of the right amount of pressure to the upper arm will often cause elevation of diastolic pressure in the brachial artery below the site of compression. In a typical experiment, two blood pressure cuffs were applied to the arm: one immediately above the elbow, the other just below the shoulder. The upper cuff was used to apply pressure, the lower for estimation of the blood pressure. With the upper cuff deflated, the blood pressure was 110/72, the "normal" blood pressure for this subject. With the upper cuff inflated to a pressure of 90 mm. Hg, which caused definite decrease in the volume of the pulse at the wrist, the blood pressure was 88/80.

3. In aortic stenosis of moderate or high grade, the diastolic pressure is often slightly or moderately elevated. This elevation is a result of decrease in the amplitude of the pulse wave due to slow systolic discharge of the left ventricle.

In some cases of coarctation, mean pressure in the femoral arteries is actually above normal, although in all cases, it is lower than mean pressure in the brachial arteries. This elevation does not necessarily signify the presence of arteriolar constriction in the lower extremities, but may just as well be due to hypoplasia and diminished capacity of the distal segment of the aorta and its branches. Such hypoplasia has been noted in many cases at necropsy.[9]

CONCLUSIONS

The evidence at hand does not afford proof for the existence of a general increase in arteriolar tone throughout the body in coarctation of the aorta. Hypertension in the arms and elevation of diastolic pressure in the legs both may be explained by the mechanical effects of the lesion. Consideration of the results of recent studies does not warrant abandonment of the concept presented in 1931 by Blumgart, Lawrence, and Ernstene.[4]

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OBSERVATIONS CONCERNING THE INFLUENCE OF CALCIUM UPON THE ACTIONS OF A DIGITALIS GLYCOSIDE

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THE possible relationship of calcium and digitalis compounds with respect to their combined effects upon the heart is still not completely known. Clark,[1] working with the frog's heart, was the first to observe that digitoxin did not affect its typical cardiac actions in the absence of calcium. Later, Ransom[2] found that strophanthin markedly improved the beating of a perfused frog's heart if the latter had been weakened previously by the removal of calcium from the perfusion fluid. Loewi[3] confirmed these results, emphasizing the similarity of cardiac effects following either the administration of strophanthin or excess calcium. It is probable that the concept of synergism between calcium and digitalis compounds had its origin in the results of these experimenters.

Later workers approached the problem by studies of the intact mammalian heart following exposure either to digitalis or calcium. Gold and Edwards,[4] working on dogs, concluded that a marked synergism existed between ouabain and calcium. Lieberman,[5] Bower and Mengle[6] McGuigan and Higgins,[7] and Smith and associates,[8,9] however, could find little evidence of any synergism existing between calcium and digitalis compounds.

In the present communication, the results of studies concerning the actions of calcium and the digitalis glycoside, lanatoside C, upon the embryonic duck heart are reported. These results indicate that the calcium ion and the glycoside are not synergistic. More important, perhaps, the results also indicate that the physiologic activity of the glycoside employed is not impaired by the *total* absence of calcium.

METHODS

The manner in which the embryonic duck heart, devoid of nervous elements,[10,11] can be employed for the study of the cardiac effects of a digitalis glycoside has already been described. In the presence of sufficient digitalis glycoside, the embryonic heart immediately increases its rate of beating, exhibiting a hypertonic type of contraction and beginning to have auriculoventricular block, then becomes irregular, slower, and finally ceases. The time of occurrence

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of A-V block and the duration of beating at any given temperature have been found [10] to bear a close quantitative relationship to the concentration of glycoside. Thus, the amount of glycoside in contact with an embryonic heart can be estimated by the chronological sequence of the development of A-V block and cessation of beating.

Tyrode's solution was employed as the basic medium, and changes in its calcium or potassium content were made either by removing or adding the chlorides of either cation. Lanatoside C (derived from *Digitalis lanata*) was used in all experiments and a fresh ampule of it was opened for each day's experiments.

RESULTS

The Effect of Variations in Calcium Ion Concentration Upon the Embryonic Duck Heart.—As Table I,*A* indicates, variations from 5.0 to 100 mg. of calcium chloride per 100 c.c. of Tyrode's solution had little effect upon the cardiodynamics of the embryonic hearts, except for a slowing of rate and slight irregularity of rhythm of hearts immersed in Tyrode's solution containing excess calcium (Table I, *A*,5). Hearts beating in Tyrode's solution containing no calcium (Table I, *A*,2), however, beat weakly, and twelve of thirty-two hearts (37.5 per cent) exhibited A-V block after an average period of fifteen minutes. In summary, at no concentration of calcium studied were hearts observed to behave like those exposed to digitalis glycoside.

TABLE I. THE EFFECTS OF VARIATIONS IN THE CONCENTRATION OF CALCIUM ON NORMAL EMBRYONIC HEARTS AND ON THOSE EXPOSED TO DIGITALIS GLYCOSIDE

	CALCIUM CONC. (MG. %)	NUMBER OF HEARTS	SIZE OF HEARTS*	RATE (PER MIN.)	A-V BLOCK (NO. HEARTS)	ONSET OF A-V BLOCK (MIN.)	RHYTHM	FORCE OF BEAT	DURATION OF CONTRACTIONS (MIN.)
A. No Digitalis Glycoside Present									
1.†	20	15	28	59	0	—	Reg.	Vig.	Over 60
2.	0	32	31	66	12	15	Reg.	Weak	Over 60
3.	5	12	29	74	0	—	Reg.	Mod.	Over 60
4.	10	8	29	74	0	—	Reg.	Mod.	Over 60
5.	100	12	29	39	0	—	Irreg.	Vig.	Over 60
B. With Digitalis Glycoside (0.001 Mg. Per c.c.)									
1.‡	20	18	31	90	18	11	Irreg.	Vig.	22
2.	0	41	28	84	12	19	Irreg.	Mod.	34
3.	5	16	22	70	10	18	Irreg.	Mod.	27
4.	10	12	24	66	12	19	Irreg.	Mod.	26
5.	100	12	29	75	12	10	Irreg.	Vig.	22

*Equals the diameter in millimeters of the vascular sinus surrounding the embryo.

†Equals a control solution or ordinary Tyrode's solution.

‡Equals a control solution of ordinary Tyrode's solution plus 0.001 mg. of digitalis glycoside per cubic centimeter.

The Effect of Variations in Calcium Concentration Upon the Activity of a Toxic Amount of Digitalis Glycoside.—The immersion of eighteen duck hearts in ordinary Tyrode's solution containing the normal amount of calcium chloride (20 mg. per cent) and 0.001 mg. of lanatoside C per cubic centimeter was found (Table I, *B*,1) to result in A-V block in each of the hearts after an average period of eleven minutes (range, nine to thirteen minutes) and in permanent cessation of beating after an average period of twenty-two minutes (range, thirteen to thirty minutes). This toxic action of the glycoside was markedly but not completely inhibited, however, if all calcium was removed from Tyrode's solution. Thus, only twelve of forty-one hearts (29 per cent) exposed to glycoside in the absence of calcium exhibited A-V block and then only after nineteen minutes (Table I, *B*, 2). This same series also continued to beat for thirty-four minutes. Hearts exposed to the same amount of glycoside in Tyrode's solution containing 5.0 or 10 mg. per cent of calcium chloride (see Table I, *B*, 3 and 4) also showed somewhat lessened sensitivity to the glycoside as compared with the control hearts. Excess calcium, however, was not found to enhance the action of digitalis glycoside, as hearts immersed in Tyrode's solution containing 100 mg. per cent of calcium chloride did not exhibit A-V block or cease beating any faster than did the control hearts (Table I, *B*, 5). These results indicated that, whereas the withdrawal of calcium from Tyrode's solution partially inhibited the action of glycoside, an excess amount of calcium did not enhance the action of the cardiac drug.

The Effect of Excess Calcium Upon the Sensitivity of the Embryonic Duck Heart to Varying Amounts of Digitalis Glycoside.—Although the foregoing experiment appeared to indicate that calcium bore neither synergistic nor specific additive relationship to the action of a digitalis glycoside, it was conceivable that the extreme toxicity of the quantity of glycoside employed precluded further acceleration of its activity, despite the type of agent added.

It was found, however, that the addition of excess calcium (100 mg. per cent) did not enhance the action of digitalis glycoside at any concentration of the latter employed (Table II). Thus, hearts exposed to 0.001, 0.0005, and 0.0001 mg. of glycoside per cubic centimeter of *normal* Tyrode's solution exhibited A-V block and cessation of beating just as often and as rapidly as did hearts exposed to the same amounts of glycoside plus excess calcium (Compare Table II, *A* and *B*). Moreover, neither hearts in normal Tyrode's solution nor hearts in excess calcium reacted to 0.00001 mg. of glycoside per cubic centimeter. These results indicated that excess calcium did not render the duck heart more sensitive to the effects of digitalis glycoside at any concentration.

The Behavior of the Embryonic Duck Heart Exposed to Digitalis Glycoside in Tyrode's Solution Without Potassium and Tyrode's Solution Without Potassium or Calcium.—The preceding experimental observations, while indicating that no synergism existed between calcium and digitalis glycoside, nevertheless also suggested that the action of the glycoside was markedly interfered with if calcium was diminished or absent. Since the withdrawal of calcium from Tyrode's solution is known to accentuate the effect of the potassium still remain-

TABLE II. THE EFFECT OF EXCESS CALCIUM ON THE SENSITIVITY OF EMBRYONIC HEARTS TO VARIOUS QUANTITIES OF DIGITALIS GLYCOSIDE

	DIGITALIS GLYCOSIDE (MG/C.C.)	NUMBER OF HEARTS	SIZE OF HEARTS*	A-V BLOCK (NO. HEARTS)	ONSET OF A-V BLOCK (MIN.)	DURATION OF CONTRACTIONS (MIN.)
			A. Hearts in Ordinary Tyrode's Solution			
1.	0.001	18	31	18	11	22
2.	0.0005	15	33	15	14	42
3.	0.0001	12	31	12	18	46
4.	0.00005	18	32	14	39	Over 60
5.	0.00001	16	28	0	—	Over 60
			B. Hearts in Tyrode's Solution With High Calcium (100 Mg. %)			
1.	0.001	12	29	12	10	22
2.	0.0005	14	22	14	12	38
3.	0.0001	13	32	12	18	41
4.	0.00005	20	28	6	45	Over 60
5.	0.00001	10	30	0	—	Over 60

*Equals the diameter in millimeters of the vascular sinus surrounding the embryo.

ing in this type of solution, it was thought possible that this last fact might well explain the diminished action of digitalis glycoside after the withdrawal of calcium. In other words, the known action of potassium in inhibiting the action of digitalis compounds[12,15] would be accentuated following the removal of calcium. Control studies were made on hearts beating in the absence of potassium and also in the absence of both potassium and calcium (Table III, *A*, 2 and 3). Auriculoventricular block and cessation of beating occurred as frequently and as rapidly in both types of solution.

Eleven hearts immersed in Tyrode's solution containing no potassium but 0.001 mg. of glycoside per cubic centimeter exhibited A-V block after five minutes and ceased to beat after seventeen minutes. These results when compared with those obtained on hearts exposed to the same quantity of glycoside in normal Tyrode's solution (compare Table III, *B*, 1 and 2) indicated that the absence of potassium markedly accentuated the activity of digitalis glycoside. Furthermore, when twenty-three hearts were exposed to the same quantity of digitalis in Tyrode's solution containing neither calcium nor potassium, it was found (see Table III, *B*, 3) that these hearts exhibited A-V block and cessation of beating as rapidly as did those immersed in Tyrode's solution containing calcium but no potassium (compare Table III, *B*, 2 and 3). In summary, calcium was not found to be necessary for the action of digitalis glycoside if potassium was absent.

TABLE III. THE EFFECTS OF POTASSIUM AND CALCIUM DEPRIVATION ON NORMAL EMBYRONIC HEARTS AND THOSE EXPOSED TO DIGITALIS GLYCOSIDE

	TYPE OF SOLUTION	NUMBER OF HEARTS	SIZE OF HEARTS	RATE	A-V BLOCK (NO.)	ONSET OF A-V BLOCK (MIN.)	DURATION OF CONTRACTION (MIN.)
	A. No Digitalis Glycoside Present						
1.	Normal Tyrode's	15	28	59	0	—	Over 60
2.	Tyrode's—No K	29	29	86	21	14	29
3.	Tyrode's—No K, No Ca	18	26	85	14	15	29
	B. With Digitalis Glycoside (0.001 Mg. Per c.c.)						
1.	Normal Tyrode's	18	31	90	18	11	22
2.	Tyrode's—No K	11	28	105	11	5	17
3.	Tyrode's—No K, No Ca	23	26	104	23	6	15

DISCUSSION

There appeared to be little doubt from our results that the action of calcium upon the embryonic duck heart was radically different from that of the digitalis glycoside employed. Likewise, no variation in calcium was found to give results which might suggest that a synergism existed between it and digitalis glycoside in their effects upon the duck heart.

Despite the lack of evidence suggesting a synergism between excess calcium and glycoside, our studies did indicate that very low concentrations of calcium in Tyrode's solution retarded the action of digitalis glycoside. This latter phenomenon was found to be due not to the absence of the calcium ion, per se, but to the relative physiologic preponderance of the potassium ion which resulted after the withdrawal of calcium. Thus, it was this accentuation of the physiologic activity of potassium with its increased inhibition of digitalis glycoside[12,13] which accounted for the diminished action of digitalis glycoside in the absence of calcium. This was shown clearly in those experiments in which hearts immersed in Tyrode's solution containing neither calcium nor potassium reacted as much to digitalis glycoside as did those immersed in Tyrode's solution lacking only potassium. It should be emphasized also that Clark[1] employed solutions containing potassium, and his withdrawal of calcium from these same solutions could have inhibited glycoside in the same indirect manner which has been discussed.

SUMMARY

The embryonic duck heart was employed for experiments in which the relationship of calcium and a digitalis glycoside was studied. It was found that the effects of this glycoside were not enhanced by excessive amounts of calcium.

Finally, it was discovered that the digitalis glycoside studied could exert its typical and usual affects in the complete absence of calcium.

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A NOMOGRAM FOR RATE CORRECTION OF THE Q-T INTERVAL IN THE ELECTROCARDIOGRAM

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TARAN and Szilagyi[1] have shown recently that prolongation of the Q-T interval is a valuable diagnostic sign of rheumatic carditis in children. It is probable that measurement of the Q-T interval will now become a routine procedure. Because it is necessary to standardize the Q-T for rate with one of several formulas which require the application of time and arithmetic, it occurred to us that a nomogram for making the rate correction would be useful.

There are several empirical formulas which may be used to standardize the Q-T interval for rate. These formulas were recently reviewed by Schlamowitz,[2] who added one of his own. The several formulas yield figures which are approximately the same. Bazett's formula[3] is the simplest and has been used more widely than any other. We chose, therefore, to use the Bazett formula in our nomogram.

Bazett's formula is $Q\text{-}T = K\sqrt{R\text{-}R}$, where $Q\text{-}T = Q\text{-}T$ interval in seconds, $R\text{-}R =$ cycle length in seconds, and $K =$ a constant. Bazett's constant K is 0.370 ± 0.024 in men and 0.400 ± 0.040 in women. In applying the formula, one compares the measured Q-T with the normal Q-T. The normal Q-T is found from the formula in which the heart cycle length and the Bazett constant are known. There are tables based on this formula which give the normal Q-T associated with a given R-R.[4] One may then compare the normal Q-T with the measured Q-T.

The formula is used more generally in another way, namely: $\frac{Q\text{-}T}{\sqrt{R\text{-}R}} = K$. The measured Q-T is divided by the square root of the measured R-R. The quotient obtained, K, is then compared with Bazett's K. This method has an advantage in that one need remember only the normal K (or K's) rather than the many normal Q-T's corresponding to various heart rates. This method was used by Barker and associates,[5] for example, in their study of the Q-T interval in hypocalcemia.

Taran and Szilagyi[1] also used this method and, in addition, introduced a new thought. He preferred to call the K the Q-T corrected for rate, or the Q-Tc.

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We feel that this concept of Q-Tc represents an advantage. Bazett's formula may thus be considered to standardize the Q-T interval to a heart rate of 60 per minute or to a cycle length (R-R) of one second.

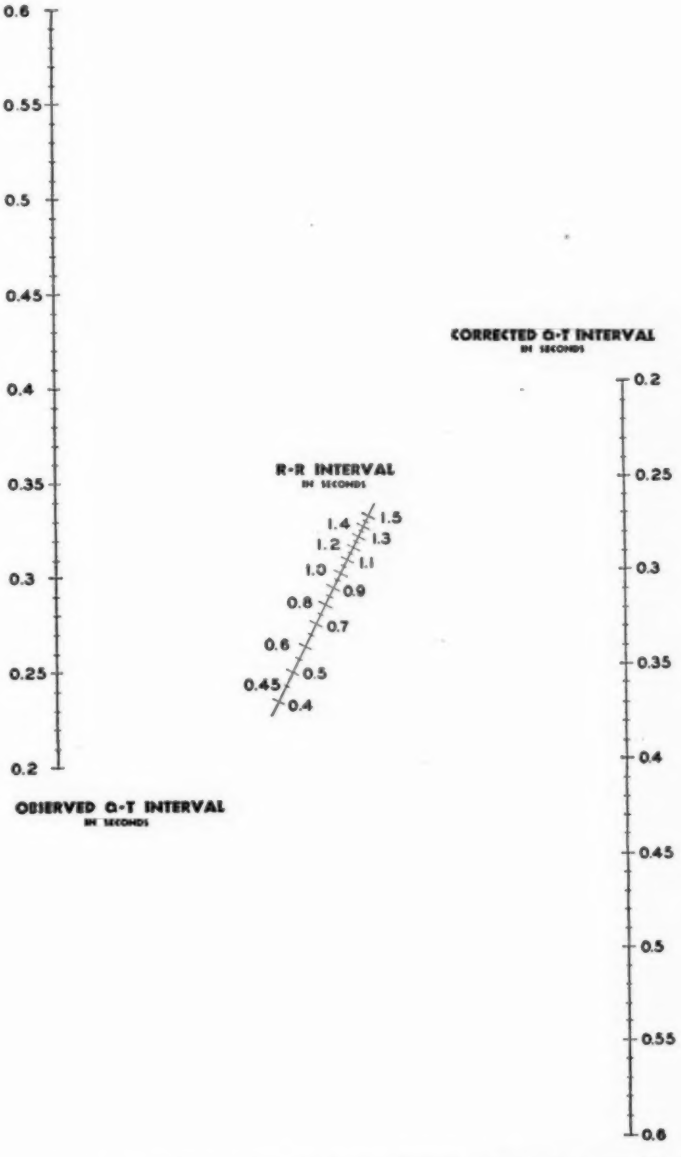

Fig. 1.—Nomogram for rate correction of Q-T interval. See text for method of use.

According to Ashman and Hull,[6] who have made thousands of measurements of the Q-T interval, the normal Q-T for an R-R of 1.0 second is: men and children, 0.386; women, 0.396. The upper limits of normal are: men and children, 0.422; women, 0.432.

The nomogram, Fig. 1, is used as follows: From the actual Q-T (left column) and R-R (central column), one may draw a line to the right column and read off the Q-Tc. This figure may then be compared with the normal Q-Tc. We have used as our straight edge a piece of vinylite or x-ray film with a scratch several inches long which has been inked in.

Instead of a nomogram, a slide rule may be used. The ordinary slide rule lends itself readily to the Bazett formula. A special slide rule could easily be devised.

The method of measurement of the Q-T interval deserves mention. The beginning of the QRS or the end of the T wave may be isoelectric in any single lead. Therefore, that lead in which the Q-T interval is longest is the proper lead in which to make the measurements. In that lead, several Q-T and R-R intervals should be measured and the resulting Q-Tc's averaged. It is incorrect to measure several Q-T intervals, then several R-R intervals, and divide the average Q-T by the square root of the averaged R-R.

SUMMARY

1. A nomogram for correcting the Q-T interval for heart rate, according to Bazett's formula, is presented.

2. The Q-T corrected for rate represents the Q-T corresponding to a heart rate of 60 (cycle length 1.0 second). It is suggested that it be known as the Q-Tc.

3. The lead in which the Q-T interval is largest is the correct lead in which to measure it.

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Clinical Reports

HEMOCHROMATOSIS WITH DEATH FROM HEART FAILURE

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UNTIL recent years, little attention was paid to cardiac symptoms as a manifestation of hemochromatosis. In Sheldon's[1] classic monograph on this disease, myocardial failure is mentioned only as an incidental cause of death. Althausen and Kerr[2] stressed the cardiac findings in three patients and suggested that, with the prolongation of life possible with insulin control of diabetes, cardiac symptoms would be found more frequently. We are in agreement with this prediction.

Blumer and Nesbit[3] and Petit[4] have reported patients with hemochromatosis with cardiac failure, and all three authors have extensively discussed this complication. Murray Lyon[5] reported three cases of patients with hemochromatosis, two of whom died of heart failure. Bloom[6] and John[7] have described patients with hemochromatosis who showed unmistakable evidence of cardiac disorder. A large group of French authors[8-15] have stressed the cardiac features of hemochromatosis and give to this symptom complex the name "syndrome endocrino-hepato-cardiaque." The most comprehensive discussions are those of de Gennes and co-workers[11] and of Oumansky and Longuet.[14]

To call attention again to the importance of myocardial changes in this disease, the following case is presented.

CASE REPORT

L. R., a 31-year-old farmer, was admitted to the Veterans Administration Hospital, Richmond, Va., on April 25, 1946, by transfer from the Medical College of Virginia Hospital. He had been admitted there on April 21 in diabetic coma, which had been successfully treated, and diabetes was fairly well controlled at the time of transfer.

The patient had regarded himself as being in good health all his life and had served in the Army from Sept. 9, 1943, until Feb. 1, 1946. During this period, he had been stationed in the Philippines and in New Guinea and had served as a cook and as a welder. He had had four Army

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hospitalizations, three for impetigo and one for stomach trouble. He knew of no urinary findings on these admissions. In November, 1945, he began to lose weight. He returned to the United States on points and received an honorable discharge Feb. 1, 1946. He stated that no urinalysis was done at this time. During the next three months he noticed nocturia, polyuria, polydipsia, increasing weakness, and weight loss of 25 pounds. On April 19 he began to be drowsy, grew nauseated and vomited, and lapsed into unconsciousness. Diabetic coma was diagnosed by his family physician and he was referred to the hospital for treatment.

On admission to the Medical College of Virginia Hospital, the patient was semicomatose, dehydrated, and exhibited Kussmaul breathing. The skin was of a dusky, brownish color, and the liver edge was palpable at the level of the umbilicus. Urine showed 4 plus sugar and 4 plus acetone. Blood sugar was 800 mg. per cent. The carbon dioxide combining power was 20 volumes per cent. During the next twelve hours, the patient received 970 units of insulin, 4000 c.c. of normal saline, and 1,000 c.c. of 5 per cent glucose in saline, with good clinical and chemical recovery from coma. The patient was placed on a suitable diet and maintained on 30 units of insulin before each meal. Hemochromatosis was suspected because of the dusky skin pigmentation and hepatic enlargement. The urine sediment was examined for hemosiderin and was reported negative. On April 25, the patient was transferred to the Veterans Administration Hospital.

On admission to this hospital, the patient was alert and in no discomfort. He was thin and emaciated, and the skin was of a dusky tan color with a suggestion of a leaden hue when the light fell across it. Blood pressure was 95/55. The liver was greatly enlarged, the firm edge being palpable at the level of the umbilicus and extending across into the left upper quadrant. The spleen was not palpable. The heart was apparently of normal size, with regular rhythm. The sounds were distant, but no murmurs were heard. The lungs were clear. Deep reflexes were hypoactive in the lower extremities. Examination otherwise was entirely negative.

The history was reviewed and was essentially as has been given. The patient stated that during his last months in the Army, friends commented on the darkening of his skin. He knew of no diabetes in his family. He had never been jaundiced.

The urine contained 4 plus sugar but no acetone, and the fasting blood sugar the day after admission was 307 mg. per cent. Hemoglobin was 100 per cent; white blood cells, 6,100 with a normal differential count. Bromsulfalein test done on May 2, using a dose of 5 mg. per kilogram of body weight, showed no retention of dye in forty-five minutes.

The patient was placed on the same diet he had been receiving, and dosage of 30 units of regular insulin before each meal was continued. Then, because of suspected liver disease, supplementary feedings of skimmed milk and choline, 6.0 Gm. daily, were added. Diabetes remained well controlled. On May 2, the patient was changed to protamine zinc insulin and was soon regulated on 15 units of regular insulin and 50 units of protamine. He was allowed up and urged to be active. His diet was gradually increased, and his insulin was increased to 20 units of regular and 60 units of protamine. With the patient's increased activity his diabetes became more difficult to control; on the same insulin dosage his blood sugar showed erratic changes, and some hypoglycemic levels were found, although no frank reactions occurred. During this period, the patient appeared to be quite well and gained in weight from 111 to 123 pounds. There was no change in the size of the liver. The blood pressure, which had been low on hospital admission, had risen to 110/70 and was maintained at this level.

On the night of May 29, the patient complained of a peculiar precordial fluttering sensation with some shortness of breath. Examination showed a tachycardia of 160 per minute with some irregularity which did not respond to carotid sinus pressure. With sedation the rate slowed and the next morning was 100, with occasional extrasystoles. Blood sugar on this morning was found to be down to 50 mg. per cent. He was given extra feedings of orange juice, and his insulin dosage was reduced. No subsequent hypoglycemia occurred. The patient, however, continued to complain of precordial fluttering and increasing shortness of breath. Electrocardiogram on May 31 showed occasional ventricular premature contractions, low voltage of the QRS complex in all leads, deep S_2 and S_3, diphasic T_1 and T_2, and inverted T_4 (Fig. 1). These changes indicated myocardial disease and an old anterior infarction was suggested.

The patient became progressively more dyspneic. By June 1 it was apparent that the liver had become larger, and extended 5 cm. below the umbilicus. Distention of the neck veins was visible even with the patient upright. The heart appeared to be enlarging. The rate remained around 100 with more frequent extrasystoles. No murmurs or rubs were heard. The blood pressure fell to 90/55. The lungs remained clear. Quinidine, 3 grains every four hours, was begun. The rhythm became more regular, but dyspnea, orthopnea, and evidence of right heart failure became more pronounced. On June 3, the neck veins were grossly distended, and with the patient recumbent, one vein in the left side of the neck became enlarged to the size of an egg. The heart appeared enlarged to both left and right. The sounds were audible, but weak. The second pulmonic sound was accentuated, but no other abnormal sounds were heard. Blood pressure varied between 90/70 and 80/60.

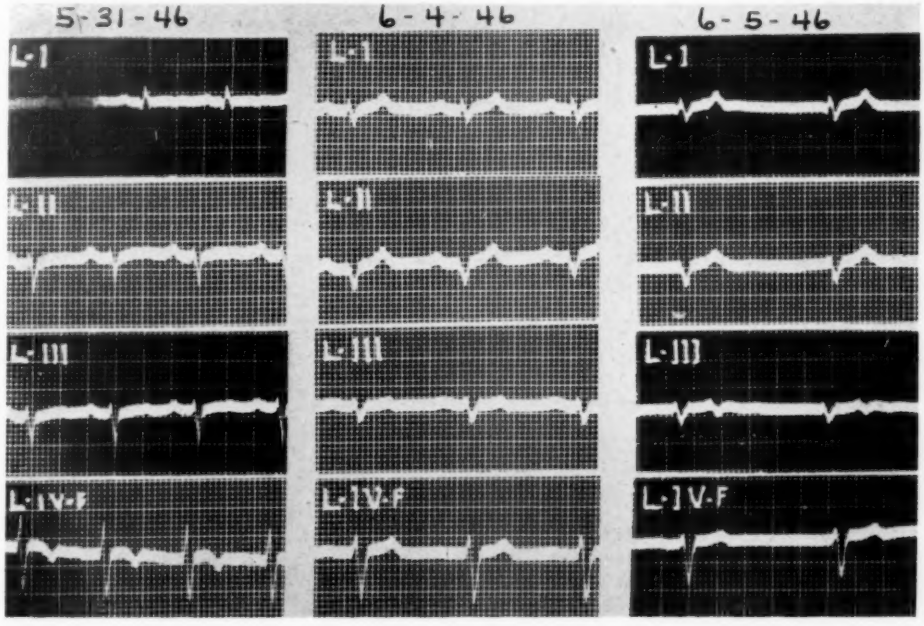

Fig. 1.—Serial electrocardiograms. On May 31, 1946, ventricular premature contractions were present but do not show on the segments reproduced here. Note the development of complete sino-auricular block in the tracing of June 5, 1946.

Pericardial effusion was suspected. Fluoroscopy and films were taken (Fig. 2). The heart was enlarged in all dimensions. Cardiac pulsations were visible, but of small amplitude. Films in the supine position revealed a peculiar widening of the mediastinal shadow which was difficult to interpret. Atelectasis of the right lower lobe with elevation of the right diaphragm was also demonstrated.

Pericardiocentesis was attempted through the xyphoid approach, but no fluid was obtained. Various diagnoses were considered, including acute cor pulmonale, myocardial infarction, right auricular thrombus formation, and others. The consensus, however, was that the patient was suffering from some type of diffuse myocardial disease with failure predominantly of the right-sided type. Hemochromatosis involving the myocardium was considered to be a likely factor, but some other acute process was thought to be present as well. Digitalis was withheld because it was considered to be of little value in this type of failure and potentially dangerous in an already irritable heart. The patient was kept propped upright in an oxygen tent, Karell feedings were given,

and Mercupurin was given for diuresis. Quinidine was continued. Regular insulin was given in sufficient amounts to prevent ketosis, but the diabetes was not strictly controlled. Large doses of thiamin were given empirically.

The patient showed no response to these measures, and his condition became steadily worse. The neck veins remained distended, the liver enlarged, and sacral and ankle edema developed. The lungs remained clear throughout. The patient remained afebrile and conscious until terminally. The pulse rate remained peculiarly slow, not exceeding 100 per minute, and was fairly regular until the end. However, cardiac action appeared to become weaker. Subsequent electrocardiograms showed low voltage and slurring of QRS complexes, return of upright T waves, and the development of sinoauricular block (Fig. 1). The peripheral pulse became more feeble, blood pressure dropped, and cyanosis developed. The patient died on June 5.

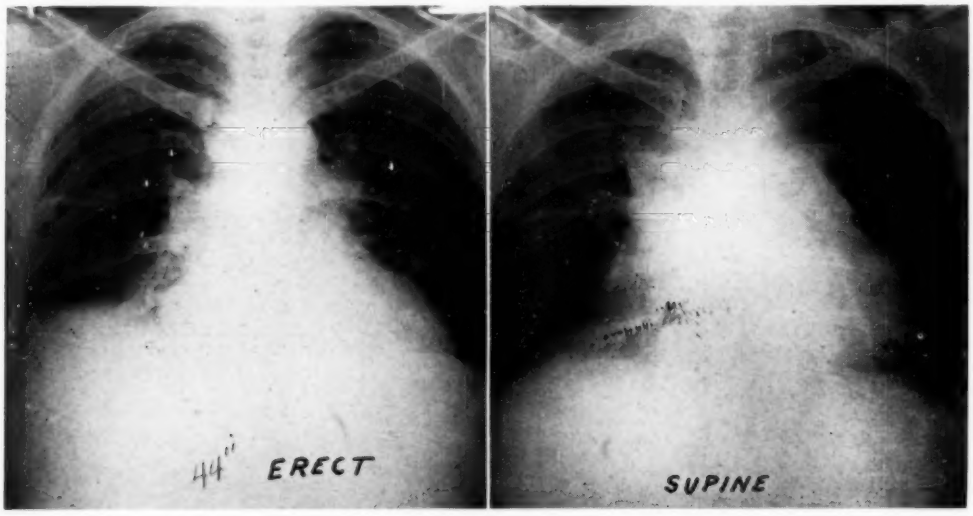

Fig. 2.—Erect and supine chest films taken at 44-inch target distance. See text for discussion.

*Autopsy Findings.**—The skin had a markedly yellow color, with a large number of frecklelike pigment spots over the entire body. The pleural cavities contained 700 c.c. of turbid yellow fluid in the right side and 400 c.c. in the left. The peritoneal cavity contained 1,000 c.c. of similar fluid. The lungs showed atelectasis of the right lower lobe and of the posterior portion of the left lower lobe. No obstruction of the bronchi or of the pulmonary vessels could be found.

The heart was dilated to a remarkable extent, filling approximately one-half of the anterior chest area. All chambers were dilated, particularly the right atrium which formed a large bulge on the right margin. The heart muscle was of a peculiar coppery brown color, and was thin and flabby. Small ante-mortem thrombi were present in the tip of the right auricular appendage and in the tip of the left ventricle, adherent to the endocardium. There was no evidence of infarction of the myocardium. The coronary vessels were patent. The heart valves were normal. The pericardial cavity contained only 15 c.c. of yellow fluid. The aorta, pulmonary vessels, and venae cavae were dissected out and showed no thrombosis. There was remarkable dilatation of the superior vena cava and of the jugular veins.

The spleen weighed 275 grams. It was soft and dark red with a congested firm pulp on section. The liver was very large, weighing 3,300 grams. It was coppery brown in color and its surface showed a coarse, granular appearance. On section, the dark brown color extended throughout, the

*Autopsy was done by Dr. George Z. Williams two hours after death.

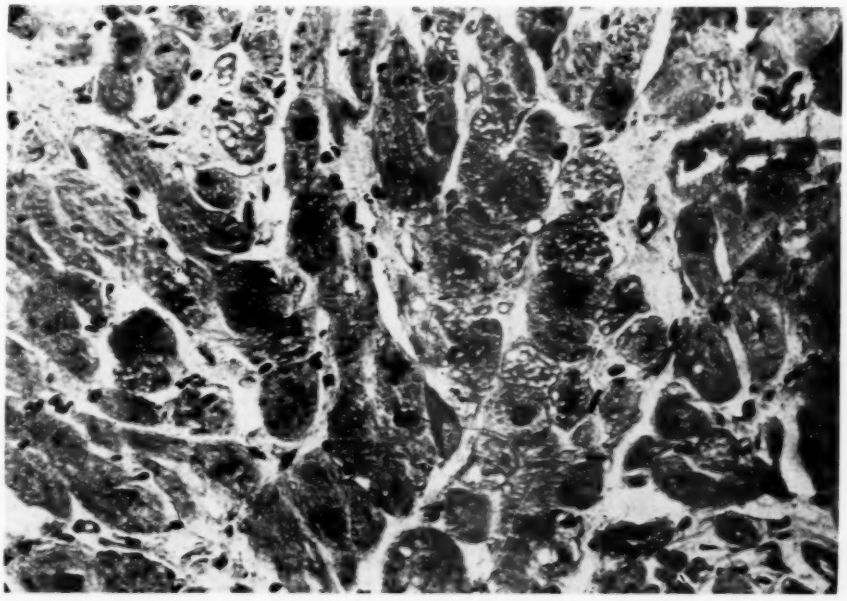

Fig. 3.—Myocardium, showing swelling and vacuolar degeneration of muscle, characteristic of the entire heart. (Hematoxylin and eosin stain, ×360.)

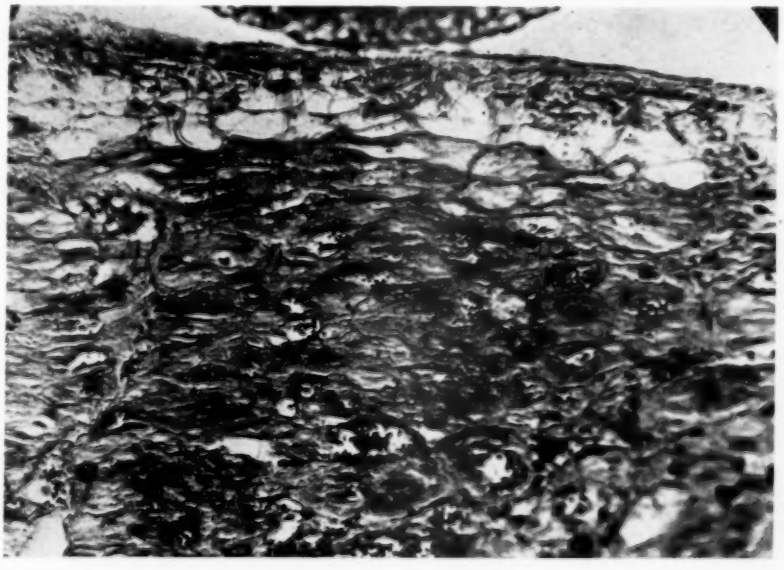

Fig. 4.—Myocardium, showing iron granule deposits in muscle fibers. (Iron stain, ×180).

consistency was firm, and interlobar markings were accentuated. The gall bladder and ducts appeared normal. The pancreas was small, weighing 100 grams, and was of a chocolate brown color. Lymph nodes in the region of the liver and pancreas were also chocolate brown in color. The kidneys, adrenal glands, and gastrointestinal tract appeared normal on gross examination and section.

Microscopic Examination.—Sections of the heart (Figs. 3 and 4) showed marked swelling of the muscle cells and considerable irregularity in the amount of connective tissue between the muscle bundles. Individual cells were lost and replaced by connective tissue, but no dense fibrosis was seen. The nuclei of the surviving cells varied considerably in size. The cytoplasm of the muscle cells was light-staining and markedly granular with much space between the fibril granules. Many of the muscle cells contained much greenish brown, fine dustlike pigment. Iron stains showed this pigment to give a positive Prussian blue reaction. In the connective tissue between the muscle cells and bundles, there were numerous endothelial-type cells and other phagocytes which also contained clumps of brown pigment yielding a positive reaction to iron stains. The vessels of the heart were not remarkable.

Sections from the atelectatic areas of the lungs showed complete alveolar collapse. Sections from other areas showed congestion and some heart failure cells, which gave the iron-positive staining reaction. Aside from these cells, no pigment deposition was seen.

Marked congestion of sinusoids and pulp of the spleen was present. Prussian blue staining revealed large amounts of iron pigment in both the endothelial cells and the connective tissue. In the lymph nodes there was marked pigmentation of the reticulo-endothelial cells and also of the elastic tissue of the media of adjacent blood vessels, giving a positive iron stain.

In the liver there was moderate increase of the connective tissue in the portal areas with distortion of the lobules caused by regenerating liver cells. The liver cells were diffusely infiltrated with large amounts of greenish brown pigment which gave a positive iron stain. Many of these cells showed swelling and other degenerative changes. Pigment was conspicuously scanty in the areas of regenerating liver cells. Pigment deposits were heavy in the Kupffer cells of the sinusoids.

In the pancreas there was considerable fibrosis in the septa encroaching on the lobules. The islands of Langerhans were conspicuously decreased in number and those remaining were either atrophic or moderately hypertrophic. Iron pigment deposits were heavy in the connective tissue and within the islet cells in fine granular form.

There were marked iron pigment deposits in the cortical cells and less marked fine, dusty deposits in the medullary cells of the adrenals. No degenerative changes of the adrenal cells were seen. In the kidneys the glomeruli were normal. Small amounts of iron pigment were seen in the epithelial cells of the Henle loop tubules.

In sections of the skin small amounts of iron pigment were seen in the basal layer of the dermis and in the subcutaneous glandular structures.

The final pathologic diagnoses were: (1) hemochromatosis with marked iron deposition and pigmentation in heart, liver, lymph nodes, adrenal, and pancreas; (2) acute cardiac dilatation due to muscle atrophy and edema; (3) pulmonary atelectasis; and (4) marked visceral congestion.

DISCUSSION

Hemochromatosis became clinically evident in this patient at an unusually early age. In Sheldon's[1] series of cases, only 8 per cent of the patients were younger than 35 years. In most of these, hemochromatosis was discovered only at post mortem, the patients having died of some other cause. It is of interest that the French authors[11,14] who describe the "syndrome endocrino-hepato-cardiaque" believe that it occurs at an age definitely below the average for most patients with hemochromatosis.

The diabetes of this patient was rapidly progressive, and he exhibited a narrow margin of balance between excessive glycosuria and hypoglycemic reactions. This is considered characteristic of the diabetes of hemochromatosis.[16,17] The instability of the blood sugar is generally attributed to the co-existing liver cirrhosis with impairment of the ability of the liver to store glycogen.

The type of heart failure that this patient showed is of interest. Failure was acute in onset, rapidly progressive, and predominantly right sided. The widened mediastinal shadow was apparently due to enormous dilatation of the vena cava and its tributaries. At autopsy, all chambers of the heart were dilated, but particularly those on the right. The myocardial pigmentation and degeneration involved all the heart muscle diffusely. We believe that this patient had total heart failure, with the clinical effects chiefly apparent on the right side because of the relative anatomic weakness of the right ventricle as compared to the left. This type of total heart failure is seen in beriberi[18] and in severe cases of acute rheumatic myocarditis.[19] In the other cases of hemochromatosis with heart failure which we have reviewed, the failure has been more often right sided, but in many, both right- and left-sided failure have occurred.

Hypoglycemia was undoubtedly a factor in initiating heart failure in our patient. However, failure was severe and progressive after the blood sugar had returned to normal. We do not believe that a temporary episode of hypoglycemia, not severe enough to produce clinical shock, could produce irreversible changes in normal heart muscle. In heart muscle already damaged nearly to the limit of functional capacity, hypoglycemia might well tip the scales to the point of failure.

Digitalis was not used in our patient. It seemed of questionable value in such acute and generalized failure, and potentially dangerous in an already irritable heart. In some of the reported cases of heart failure in hemochromatosis, digitalis has been temporarily effective,[2,12,13] but in the majority of these patients, it has proved of no value.[1,11,14,15]

Petit[4] has called attention to the frequency of cardiac arrhythmias when the heart is involved in hemochromatosis. In the twenty-one cases that we have reveiwed, complete heart block is described four times,[2,4,11] paroxysmal auricular tachycardia twice,[5,6] and auricular fibrillation once. Many of the other patients exhibited frequent extrasystoles.

The French authors[11,14] do not believe that heart failure in hemochromatosis can be attributed to damage to the heart muscle caused by pigment. They call attention to the frequency with which extensive pigment deposition in the heart is seen without heart failure. They have advanced the hypothesis that heart failure is caused by some unknown type of endocrine disturbance[11] or, more specifically, by adrenocortical deficiency.[14] However, in all the cases reported in the English literature, extensive myocardial damage has been described, presumably resulting from pigment deposition. Althausen and Kerr[2] found diffuse myocardial sclerosis; Blumer and Nesbit,[3] extensive fibrosis; Petit,[4] areas of muscle atrophy and fibrosis; Bloom,[6] vacuolization and fibrillar lysis; and John,[7] extensive fatty degeneration. Our patient showed extensive degenerative

changes as well as pigment deposition in the heart muscle. We believe that these changes are sufficient to explain the cardiac failure. The adrenal glands contained pigment but showed no degenerative changes, and clinically, there was little to suggest adrenocortical insufficiency. The findings in our patient do not support the French point of view. We would agree with Blumer and Nesbit[3] that when pigment deposits in the myocardium become severe enough to produce cellular degeneration, function is interfered with and heart failure can result.

CONCLUSIONS

1. A case of hemochromatosis with death from heart failure is reported.
2. The importance of myocardial damage in hemochromatosis is stressed.
3. The clinical features of the heart failure and the mechanism of its production are discussed.

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PAROXYSMAL TACHYCARDIA IN THE NEWBORN

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ALTHOUGH tachycardia with very rapid ventricular rates is not common in infants and children, when it does occur it may menace the life of the infant and, therefore, demands prompt and sometimes vigorous treatment. Hubbard[1] reviewed nineteen cases of paroxysmal tachycardia in infants under one year of age and has reported nine cases in infants under eight months of age. Among sixteen patients treated with digitalis, there were fifteen who recovered and one who died as a result of proven sarcoma of the conduction system. Howard[2] reported a case of paroxysmal tachycardia in a 4-day-old infant who was treated with digitalis and recovered. Tarnower and Lattin[3] described two cases of tachycardia, in one of which auricular flutter was present and in the other, atrioventricular tachycardia of nodal origin. The first case is of interest in that the rate varied from 140 to 225 per minute and was recognized before birth. The tachycardia persisted after birth and electrocardiographic studies revealed auricular flutter with varying degrees of block. Taran and Jennings[4] have described a case of paroxysmal atrioventricular nodal tachycardia in a newborn infant, and emphasize the rarity of this disturbance by pointing out that it occurred only four times in sixteen years at the Massachusetts General Hospital.

We present the following case of a supraventricular tachycardia in a newborn infant, which produced alarming heart failure and was associated with a *Streptococcus viridans* infection in blood and urine.

CASE REPORT

R. W., a boy, was born at the Rockaway Beach Hospital July 3, 1946. The mother's pregnancy and labor were uneventful and the baby's condition at birth was normal. Both parents and three siblings were alive and well. There were no significant familial diseases. The patient's weight at birth was 8 pounds, 14 ounces. He was treated in accordance with the usual nursery routine. On the third day, the baby's temperature was 101° Fahrenheit. Examina ion at this time was negative. The possibility of dehydration fever prompted a hypodermoclysis. Twelve hours later, the infant became apathetic, the cry was feeble, and the respirations were shallow and rapid. For the first time cyanosis was present. Examination revealed a rapid heart rate, estimated to be over 200 beats per minute (Fig. 1). The rhythm was regular. Pressure over the carotid sinus brought an immediate response. The rate slowed to 130 beats per minute. With the slowing of the rate, the cyanosis disappeared and the respirations returned to normal. Ten

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minutes later, the tachycardia recurred but carotid sinus pressure at this time failed to influence the rate. The cyanosis reappeared, basal râles appeared in both lungs, and the liver edge became palpable below the costal margin. Mecholyl, 0.1 mg., was given subcutaneously and had no effect on the rate. Digitalis was then given parenterally in the following schedule, one-half cat unit

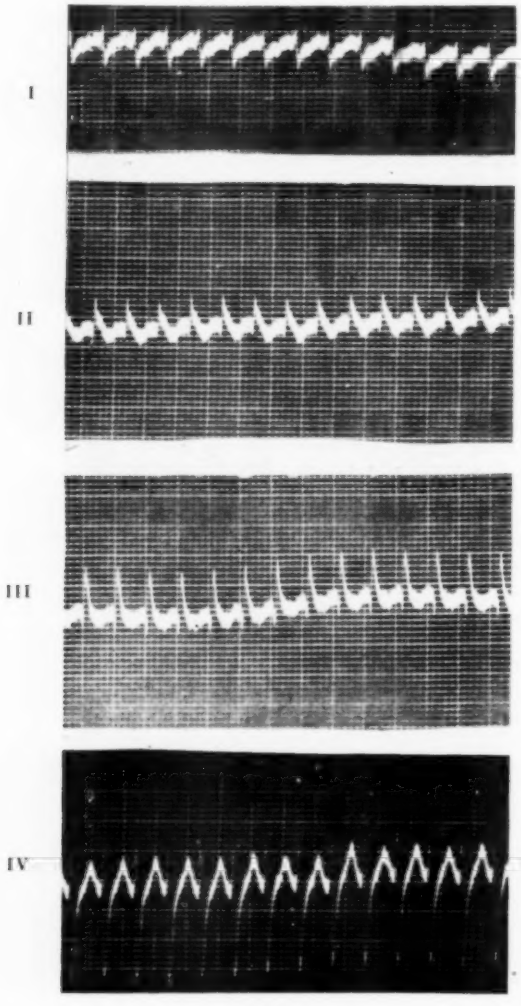

Fig. 1.

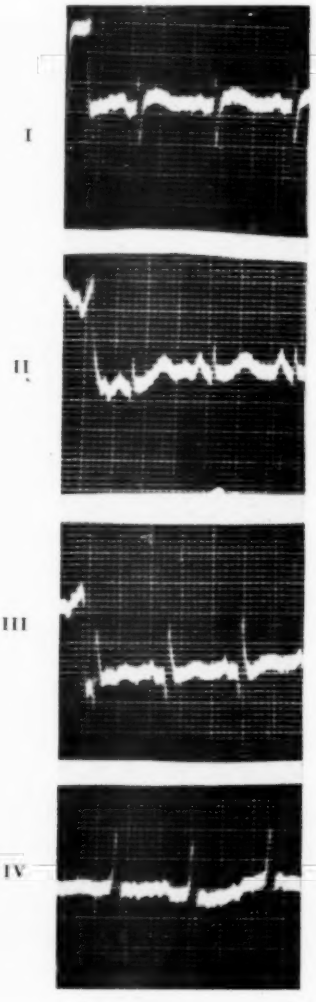

Fig. 2.

Fig. 1.—Electrocardiograph taken three days after birth. Auricular and ventricular rates 280 per minute. Sign of congective failure present.

Fig. 2.—Electrocardiogram taken thirteen days after birth. Auricular and ventricular rates 130 per minute. Normal sinus rhythm. No evidence of congestive failure.

was given immediately. Four hours later, one-fourth of a cat unit was given. The latter dose was repeated four hours later. One-quarter cat unit was then given twice a day for four days. After one cat unit had been administered, the rate of the heart returned to normal and the signs of congestive failure disappeared (Fig. 2). At the end of four days the digitalis was stopped and the heart rate remained normal.

The temperature could not be explained on the basis of the physical examination of the patient. A catheterized specimen of urine revealed numerous clumped pus cells. A pure culture of *Streptococcus viridans* was grown from the urine. A blood culture also showed the presence of *Streptococcus viridans*.

The patient was given 10,000 units of penicillin intramuscularly every three hours. Sulfadiazine, 2 Gm. per pound of body weight per day was also given. The temperature returned to normal in twenty-four hours but the blood cultures remained positive for one week. The urine was free of pus but urine culture still showed the presence of *Streptococcus viridans*. At the end of one week, the penicillin was discontinued. Sulfadiazine was continued for four weeks, at the end of which time the urine cultures became negative. At this period the cardiac status was normal and the child appeared clinically well. The weight at this time was ten pounds.

Blood chemistry showed the following values: nonprotein nitrogen, 40 mg.; sugar, 70 mg.; chlorides, 680 mg.; and cholesterol, 165 mg. per 100 c.c. of blood. Intravenous pyelography was negative. X-ray study of the chest showed a slightly enlarged cardiac shadow. The lungs were clear. There was no evidence of an enlarged thymus. A blood count, made on July 6, 1946, showed 14 Gm. of hemoglobin, 5,320,000 red blood cells, and 20,000 white blood cells. The differential count showed 47 per cent segmented and 10 per cent nonsegmented neutrophiles, 6 per cent eosinophiles, and 37 per cent lymphocytes. On July 25, 1946, the blood count showed 9 Gm. of hemoglobin, 21,450 white blood cells, and 3,180,000 red blood cells. The differential count showed 76 per cent segmented and 12 per cent nonsegmented polymorphonuclear neutrophiles, 1 per cent eosinophiles, and 11 per cent lymphocytes. A urinalysis done on July 11, 1946, was unimportant except for the presence of three to four red blood cells per high-power field and four to six white blood cells. Blood cultures made on July 9 and July 15, respectively, were positive for alpha *Streptococcus viridans*. A blood culture made on July 17 was negative. Urine cultures taken on July 15 and July 20 were positive for alpha *Streptococcus viridans*. On August 13, the urine culture was negative.

DISCUSSION

The nature of the tachycardia in this case cannot be positively identified. Auricular flutter with a 1:1 A-V ratio seems to be the most probable diagnosis. However, this condition cannot be positively established, nor can auricular or nodal paroxysmal tachycardia be eliminated. The only conclusions that can be drawn are that the tachycardia was not ventricular in origin and that it was dependent upon an ectopic rhythm; the latter seems to be well established by the prompt response to digitalis.

In spite of the uncertainty of the nature of the tachycardia, two facts stand out clearly: (1) the rapid ventricular rate produced a serious degree of heart failure and constituted a serious threat to life; and (2) the disturbance yielded promptly to digitalis. The use of digitalis in infants is not without danger.[5-8] We, therefore, used the drug in this case in what seemed to us to be a cautious and safe manner.

A connection between the streptococcus infection and the tachycardia is difficult to establish. For this reason, the infection which yielded promptly to appropriate treatment has been presented as an incidental finding. The only fact that suggests a more direct causative relationship of the infection to the tachycardia is the fact that there was no return of the tachycardia after the elimination of the infection.

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Abstracts and Reviews

Selected Abstracts

Baker, E. C.: Clinical and Roentgenologic Evaluation of Venography. Am. J. Roentgenol. **58**:603 (Nov.), 1947.

One thousand twenty-seven venograms were done with Diodrast as a contrast medium without any severe reaction. Twenty cubic centimeters of opaque material were injected during three minutes or more through a 25 or 26 gauge needle. Venipuncture was made through the skin in any vein below the ankle. A tourniquet was used only to aid in visualizing the vein and was removed before the injection was made. Three sets of stereoscopic exposures were made. One set covered an area from the ankle to the knee; a second set, the area of the upper leg, knee, and lower thigh; and the third set, the area of the upper thigh and lower pelvic area. The first exposure was made after the injection of approximately 8 c.c. (forty to sixty seconds after the start of the injection). The other exposures in succession were completed approximately at the time the injection was completed. With each exposure the quantity injected and elapsed time from the start of the injection were recorded.

Normal Subjects.—The greater portion of the contrast material enters the deep circulation fairly close to the ankle. A smaller quantity spreads through the superficial veins demonstrating external veins to the knee; usually the greater saphenous is well visualized. Young persons have straight veins and the Diodrast passes more rapidly upward than in older people who have slightly tortuous or dilated veins. In numerous normal subjects who remain motionless in the recumbent position the Diodrast may remain in the deep veins for five to twenty minutes after the injection. Any muscular activity forces the contrast material immediately upward.

Pathologic Findings.—In acute superficial block, the deep circulation is visualized up to the femoral fossa. The opaque material is seen in the superficial plexus to the site of the block. In another type of acute superficial block short lengths of straight, nondilated veins extend upward and apparently fade out. Two to four venograms showing the fading-out effect at same point should be done to confirm this finding.

In chronic superficial block, the veins are dilated and tortuous and the passage of the opaque material is usually slow. Small connecting veins extend inward toward or outward from the deep circulation for 1.0 to 3.0 cm. and appear to end abruptly in the tissues. Certain areas of superficial circulation are not demonstrable.

In acute partial or complete block of the deep circulation, definite evidence of acute superficial block is always demonstrable. The deep circulation of the involved area cannot be visualized.

In chronic block of the deep veins the deep vessels are partially or completely absent. The opaque material enters branches of the internal saphenous vein promptly, and by the time the region of the knee is reached all the contrast medium is returning upward through that vein. The entire saphenous vein is dilated and tortuous to the femoral fossa. Short lengths of communicating veins emerge from the internal saphenous vein and fade out into the tissues.

Complete block of the entire deep circulation of the leg and thigh frequently shows large dilated superficial varicosities.

Thrombi produce three types of shadows: In incomplete block, the head of the opaque column is usually concave; when the vein is incompletely obliterated a ragged, irregular area extending for a varying length is seen; finally, the opaque material may outline the walls and show a mass within the lumen.

Satisfactory venographic information can be obtained in probably 60 to 90 per cent of cases. Discontinuation of the study too soon in pathologic cases or improper timing of the exposures may possibly account for the greater percentage of failure to obtain adequate information. Blocked vessels or other roentgen findings account for additional failures.

ZION.

O'Loughlin, B. J.: Roentgen Visualization of the Inferior Vena Cava. Am. J. Roentgenol. **58**:617 (Nov.), 1947.

The author outlines a simple and safe procedure for visualizing the inferior vena cava. No serious ill effects were encountered in fifty consecutive cases. The patient is prepared in a manner similar to that used in intravenous urography. Sphygmomanometer cuffs are placed about the thighs as proximal as possible, leaving room for femoral venepuncture. The pressure in the cuffs is adjusted to diastolic pressure or slightly higher. Twenty cubic centimeters of a 35 per cent Diodrast solution are injected through a 18 gauge needle on the side selected. The rate of injection is approximately 1.0 c.c. per second. The usual kidney-ureter-bladder exposures are made outlinging the common iliac veins and inferior vena cava. Having the patient hold his breath during the exposure and injection tends to make the blood column move more slowly and smoothly. A Valsalva effort may reverse the flow sufficiently to outline the branches of the iliac veins. The removal of the cuffs releases the dammed-up venous blood from the lower extremities and may wash out or dilute the slightly thrombogenic influence of the Diodrast.

ZION.

L'Farinas, P.: Abdominal Venography. Am. J. Roentgenol. **58**:599 (Nov.), 1947.

The author described a technique of abdominal venography. Under local anesthesia the long saphenous vein is exposed by a small incision at the inner portion of the middle third of the thigh. A tourniquet at the groin permits better visualization of the vein which is then punctured with a small trocar. The tourniquet is released and 40 c.c. of Diodrast is rapidly injected into the vein. Two 14 by 17 inch film exposures of the abdomen are made. The first was made when 20 to 25 c.c. of the opague material has been injected and the second immediately after the completion of the injection. Normal venography visualizes the femoral, external, common iliac veins, and the inferior vena cava. Compression of the epigastric region with an inflated balloon may permit visualization of the renal, hepatic, and internal iliac veins.

Indications for abdominal venography are: (1) obstruction or thrombosis of the inferior vena cava; (2) abdominal tumors, especially renal neoplasms where intravenous urography is indicated; (3) liver conditions that lead to portal hypertension with the possibility of a portal vein-vena cava anastomosis in order to determine the integrity of the vena cava.

In thrombophlebitis the site of obstruction of the vessels can easily be demonstrated. In tumors that compress and displace the inferior vena cava and common iliac veins, the site of compression and displacement together with the establishment of collateral circulation can be demonstrated.

ZION.

White, P. D.: The Management of Hypertension. Ann. Int. Med. **27**:740 (Nov.), 1947.

This is a brief reveiw of therapeutic methods which have proved to be of some value in the management of hypertension. There is a short summary of the value of education of the patient concerning the true meaning of an elevated blood pressure and of the effectiveness of vacations, a regulated mode of living, mental relaxation, physiotherapy, and intensive psychotherapy. The importance of restriction of tobacco, coffee, and tea is stressed. The use of the low-salt diet or the strict rice diet is looked upon favorably. Aside from the sedation accomplished by

bromides or phenobarbitol, drugs seem to occupy a small place in the management of hypertension. It is too early to decide upon the merits of the newer sympathetic olytic drugs, such as tetraethyl ammonium and Priscol. Of the surgical approaches, the extensive lumbodorsal sympathectomy advocated by Smithwick has proved to be worth while in about 75 per cent of the properly selected cases.

WENDKOS.

Ray, C. T., and Burch, G.: Vascular Responses in Man to Ligation of the Inferior Vena Cava. Arch. Int. Med. **80**:587 (Nov.), 1947.

The authors investigated the circulatory adjustments in twelve patients following ligation of the inferior vena cava in the treatment of pelvic thrombophlebitis. In all instances but one, there was an elevation in venous pressure in the lower extremities and a gradual decline toward normal in the subsequent years of observation. A tendency for the plasma protein content to increase was also noted after ligation.

With regard to clinical observations, no diminution in functional capacity was observed, nor was any intermittent claudication experienced. The severity of the edema varied from mild to extreme, disappearing within two months after operation in all cases but three. For the most part, the large veins of the legs and feet were not dilated, and no demonstrable varicosities were noted. Some small varicosities were present in the cutaneous veins. The superficial veins of the abdominal wall and gluteal region and also the long thoracic veins were dilated, forming an unusually prominent network.

The authors concluded that remarkable readjustments occur in the lower extremities after ligation of the inferior vena cava. The fact that the edema disappeared at a time when the venous pressure in the lower extremities was still considerably elevated appeared to support the view that hydrostatic intravascular pressure, per se, plays a relatively unimportant role in edema formation, and that as long as only the hydrostatic pressure is increased, compensatory mechanisms develop to a high degree.

ABRAMSON.

Magner, D., and McKenzie, H. F.: Cystic Medionecrosis of the Aorta. Arch. Path. **44**:485 (Nov.), 1947.

The authors report a case of large, fusiform aneurysm of the ascending arch of the aorta in a 23-year-old man in whom death occurred as a result of perforation into the pericardial sac with resulting tamponade of the heart. The patient, first seen two years previously because routine x-ray examination revealed a large mediastinal mass, had had no relevant past medical history, except that at the age of 18 years, after playing hockey, he had had severe retrosternal pain for three days. There was no traumatic incident. Repeated x-ray examinations showed a gradual increase in the size of the mediastinal mass, which was seen to pulsate in the fluoroscopic examination. Serologic tests were negative and the patient worked in good health for three years following the initial discovery of the aneurysm.

A few days after a bronchoscopy which showed pulsation in the trachea, the patient collapsed and died with a perforation of the aneurysm into the pericardium. Unfortunately, no blood pressure record was obtained. Laboratory data revealed nothing of note.

At necropsy the heart was found to be of normal weight and showed no abnormality. The aortic valve leaflets were described as normal, despite the close proximity of the aneurysm, which involved the ascending and transverse portion of the arch. Detailed histologic examination revealed characteristic changes of cystic medionecrosis and excluded syphilis as an etiological factor. The authors comment on the complete lack of knowledge of the origin of this lesion.

GOULEY.

Kobernick, S. D.: Gumma of the Coronary Artery, Myocardial Infarction and Gumma of the Heart. Arch. Path. 44:490 (Nov.), 1947.

The author presents the first recorded case of myocardial infarction due to coronary thrombosis secondary to syphilitic gummatous coronary arteritis. He emphasizes the generally known fact that syphilitic aortitis often narrows and sometimes closes the coronary orifices, and that syphilitic coronary arteritis seldom involves more than the first centimeter of the two main arteries.

This unique case was that of a 44-year-old white man, serologically positive, with signs of aortic regurgitation, who was hospitalized because of severe epigastric pain accompanied by sweating. The heart sounds became distant and a gallop rhythm was present. The electrocardiogram showed evidence of an acute posterior myocardial infarction. Death occurred on the day after admission.

Autopsy revealed an enlarged heart with hypertrophy of the left ventricle associated with syphilitic aortitis and aortic regurgitation. Multiple aneurysms were noted in the aortic arch. Gummatous masses were found in the pulmonary conus and the pulmonary artery. A necrotic degeneration in the upper portion of the posterior wall of the left ventricle which extended into the adjacent ventricular septum was microscopically a myocardial infarction. Examination of the nutrient artery, namely, the right coronary, showed marked narrowing beyond its orifice for 2.0 cm. by eccentric grey-white thickening of the vessel wall. The narrowed lumen was completely blocked with red-brown thrombus. Microscopically the arterial thickening was found to be a gumma, involving the adventitia and the media, and extending into the intima. The accompanying photomicrograph shows a typical coagulative necrosis (gumma) involving the entire thickness of the wall of the right coronary artery.

GOULEY.

Wagner, F. B., Price, A. H., and Swenson, P. C.: Abdominal Arteriography. Am. J. Roentgenol. 58:591 (Nov.), 1947.

The patient is prepared by enemata in the morning of the examination and food is withheld. Preanesthesia medication of morphine and atropine is given forty-five minutes before the procedure. A preliminary exposure of the abdomen is made to check proper cleansing of the colon and correctness of the exposure factors. The patient is lightly anesthetized with 2.5 per cent pentothal sodium solution. A second anesthetist administers oxygen from a gas machine.

A special aortic puncture needle, 18 gauge and at least 15 cm. in length (malleable needle), is used. Antiseptic preparation of the back is done in the usual manner. The skin is pierced just below the left twelfth rib, four fingerbreadths from the spinous process. The needle is directed anteriorly, medially, and cephalically toward the body of the twelfth vertebra until bone is encountered. The needle is then withdrawn 2.0 cm. and the point directed more laterally so as just to slip by the body of the vertebra. The stilet is removed and the needle advanced cautiously into the aortic lumen. (When the aorta is pierced there is a sensation similar to that encountered in piercing the dura in spinal puncture.) After the needle has entered the aorta it is advanced an additional 0.5 centimeter. A pulsating drip of bright red blood rather than spurting is encountered. The needle is connected to two feet of rubber tubing and a Luer-lock syringe. Alternating injection of saline and withdrawal of blood are performed in order to assure proper function of apparatus and correct position.

A trial injection of 12 c.c. of saline solution is performed. If the test is satisfactory, 12 c.c. of 80 per cent sodium iodide solution is injected at the rate of 2.0 c.c. per second. The roentgen exposure is made as the last 1 to 2 c.c. are leaving the syringe. The needle is immediately withdrawn following the exposure.

The sodium iodide is freshly prepared and sterilized the day preceding the examination. A 70 per cent Diodrast solution has proved to be unsatisfactory. Following the examinations, one liter of 5 per cent glucose in normal saline solution is administered through the intravenous anesthesia needle. After two hours the patient is allowed a regular diet and walking is permitted if there are no other contraindications. No untoward reactions have occurred in a series of twenty-six cases.

For visualization of the celiac axis and branches, puncture is best performed at the twelfth dorsal vertebra. For visualization of the renal vessels, aortic puncture should be made one vertebra lower. For the iliac vessels and branches, puncture may be performed at the level of the second or third lumbar vertebra. Puncture at the lower levels is more difficult and it is necessary to enter the skin at six fingerbreadths from the spinous process.

Aneurysms and aortic occlusions are well demonstrated by this procedure. The method also lends itself to excellent visualization of the iliac and femoral arteries. Abdominal aortography is also of value in the diagnosis of certain abdominal tumors, particularly retroperitoneal masses of renal or adrenal origin.

ZION.

Katz, L. N.: A Survey of Recent Developments Concerning the Concepts of Coronary Disease and Its Management. Ann. Int. Med. 27:705 (Nov.), 1947.

The prognosis and management of coronary insufficiency depend on a knowledge of the natural history of coronary disease and of the factors involved in the control of the coronary circulation. Coronary sclerosis leads to ill effects by handicapping the adjustments of coronary vessels to the needs of the heart for varying amounts of blood flow. There are compensatory blood channels (the intercoronary communications, arteriovenous anastomoses, Thebesian vessels, and extracardiac collaterals) which enlarge and take over the supply of blood to the region whose coronary artery is occluded or narrowed. The adequacy of this auxiliary blood supply depends most of all upon the rapidity of the narrowing of the coronary arteries.

Age is of some importance because the coronary arteries are more nearly end arteries functionally in the young than in the old in whom these auxiliary channels have had time to develop. In the present state of our knowledge, it is not yet justified to advocate a cholesterol-poor diet in man in the hope of retarding atherosclerosis because there is reason to believe that endogenous cholesterol produced even on a cholesterol-poor diet may still lead to atherosclerosis.

Other factors besides the architecture of the coronary vessels are involved in determining the adequacy of coronary flow. It is for this reason that the term coronary insufficiency to express an inadequate coronary flow has been created and has gained wide vogue recently. The dynamic or physiologic concept serves a useful purpose in that it permits the clinician to judge whether the coronary system is able to nourish the heart adequately. Coronary insufficiency, therefore, is really to be expressed in terms of relative insufficiency. Coronary insufficiency may be focal or generalized, transitory or protracted. The transitory and the protracted forms of coronary insufficiency are often superimposed upon chronic coronary insufficiency and may be the terminal event. Focal coronary insufficiency is more likely to lead to myocardial infarction, while generalized insufficiency is more likely to lead to chronic or acute heart failure.

Except in the subendocardial layers of the ventricular myocardium, coronary blood flow is increased during the phase of cardiac systole. There is also a direct relationship between coronary flow and the cardiac output. This relationship is unaffected by the change in blood pressure. The role of vasomotor influences in altering the caliber of the coronary vessels is also discussed, and the author makes a special point of emphasizing that the vagus nerve is not a coronary constrictor but rather a coronary dilator. It is his opinion that vasoconstriction of neurogenic origin results from sympathetic overstimulation and not vagal overactivity. For this reason he questions the value of atropine sulfate in the treatment of acute myocardial infarction or acute pulmonary embolism. The author refers to experimental work which indicates that the nitrites and papaverine are the most powerful coronary dilators, whereas xanthines are very much weaker. He also observes that potassium in large doses, Pitressin, and foreign species of blood are powerful vasoconstrictors. The significance of electrocardiographic changes which follow a standard exercise test in so far as it relates to the diagnosis of coronary insufficiency is briefly discussed. The factors and mechanisms responsible for pain in coronary artery disease are amply reviewed, and the importance of such knowledge in relation to the diagnosis of coronary artery disease is emphasized. In the discussion concerning prognosis, it is pointed out that about one-fifth of the patients with recent myocardial infarction died during their hospital stay; that the average expectancy of life following an infarct is five years, but that the scatter is quite large and some

patients have lived very comfortably for over twenty years following an infarction. The factors which determine the prognosis in recent myocardial infarction and in other forms of coronary artery disease are admitted to be still poorly understood and, therefore, make it impossible to prognosticate accurately in any given patient. It is pointed out that those patients who develop a marked drop in blood pressure or go into shock have a poor prognosis and that the development of congestive heart failure or the presence of diabetes adds to the gravity of the outlook. The author recognizes that many people have had infarcts without any symptoms, without any special medical care, and the evidence of this was written in their hearts and revealed at necropsy sometime later when they died of some other circumstance or of a new infarction. He concludes that infarction is statistically more benign than is generally appreciated, that it is a self-limited disease, and that it is a process which by the time the clinician sees the case, is already a matter of convalescence, that four of five patients will survive the episode, and that most of them will have little if any handicap. Some will develop chronic coronary insufficiency, but others will be completely restored and will have, at most, only the psychological fear that all lay people and too many physicians attach to coronary episodes. In the concluding portion of the paper, there is a lengthy discussion based on modern physiologic concepts, concerning the treatment of patients with the manifestations of acute and chronic coronary insufficiency.

WENDKOS.

Rich, A. R., and Gregory, J. E.: Experimental Anaphylactic Lesions of the Coronary Arteries of the "Sclerotic" Type, Commonly Associated With Rheumatic Fever and Disseminated Lupus Erythematosus. Bull. Johns Hopkins Hosp., 81:312 (Nov.), 1947.

Forty-five rabbits were sensitized to horse serum in a manner known to be favorable to the production of the serum sickness type of protected anaphylactic reaction both in man and rabbit, namely, the intravenous injection of large amounts of the antigen. A group of eighteen male albino rabbits, weighing approximately 200 grams each, were kept as controls. Male albino rabbits, averaging about 2 kilograms in weight were used in the experiments. Sterile horse serum without preservative was injected into the ear vein in a dosage of 10 c.c. to 15 c.c. per kilogram. Seven of the forty-five animals received only a single injection; twenty-five received two injections; and thirteen received five to ten injections at various intervals. The animals were killed at periods between 17 and 364 days following the first injection of serum, and the coronary arteries were studied in appropriate sections of the heart.

All of the animals in which lesions of the coronary arteries were found at autopsy had developed the serum sickness type of reaction (fever, erythema) following one or more of the intravenous injections of serum, but arterial lesions were not found in all animals which had exhibited this type of reaction. Eighteen of the forty-five sensitized rabbits developed lesions of the coronary arteries of the type familiar in rheumatic fever. Three of the eighteen that developed the coronary lesions had received only one injection of horse serum; thirteen had received two injections; one had received five, and one nine injections. No lesions of the coronary arteries were found in any of the control animals. Fibrotic intimal lesions, similar to those occurring in the coronary arteries, were found in peripheral arteries of some of the sensitized animals.

These authors make the point that the same type of "sclerotic" lesions of the coronary arteries which are observed in disseminated lupus erythematosus, in rheumatic fever, and in periarteritis nodosa were also found in the animals subjected to experimental serum sickness.

BELLET.

Ruzicka, E. R., and Nicholson, M. J.: Cardiac Arrest Under Anesthesia, J.A.M.A. 135:622 (Nov. 8), 1947.

In the past five years the authors studied nine cases of cardiac arrest, which occurred under anesthesia. The following factors were considered to be of etiological significance in the production of cardiac arrest: The ability of cyclopropane, chloroform, and ethyl chloride to sensitize the heart to epinephrine; excitement also causes an outpouring of epinephrine into the circulation; barbiturates given intravenously and cyclopropane exhibit a parasympathetic effect on

the heart; stimulation of the vagus nerve may cause a powerful inhibitory effect on the heart. It is likely that one or more of the aforementioned factors is present in every instance of sudden cardiac arrest during anesthesia. The authors point out that treatment to be effective must begin within three to five minutes after cardiac arrest. They present the following plan of action: (1) The anesthesiologist must immediately begin artificial respiration with 100 per cent oxygen. (2) The surgeon must begin cardiac massage immediately. (3) Drug therapy consists of the use of two drugs: procaine and epinephrine. (4) General methods of treatment include the intravenous administration of fluids and the institution of 5 to 10 degrees of Trendelenburg position.

In the authors' series of nine cases the heart was revived in every instance. There were three complete recoveries and one apparent recovery but with death of the patient on the second postoperative day from acute cardiac failure. Although cardiac activity was resumed in the remaining five cases, none of the patients regained consciousness. Ventricular fibrillation is reported to be the most frequent complication occurring in cardiac resuscitation, and is fatal unless quickly corrected. This is first attempted by cardiac massage; another method is by electrical countershock. Death often occurs during the period of one to fifteen days after operation. During this time these patients show every evidence of damage to the brain. Many times the gross pathologic changes are the result of rough or forceful cardiac massage. Those patients who recover have a constant loss of memory for events twenty-four hours previous to operation. The repeated incidence of normal survival appears to be 10 per cent or less in cases of cardiac arrest. The normal survival rate in the author's experience is approximately 33.33 per cent.

BELLET.

Shumacker, H. B. J.: Surgical Cure of Innominate Aneurysm: Report of a Case With Comments on the Applicability of Surgical Measures. Surgery **22**:729 (Nov.), 1947.

This author found in the literature reports of thirty-seven attempts on direct operative attack on aneurysms of the innominate artery. Only nineteen patients survived and not all of them have been cured. There are several difficult aspects to the surgical management of this lesion, one of the most serious being the matter of exposure. Shumacker employed a sternum-splitting incision, supplemented by subperiosteal resection of the medial third of the right clavicle, which allowed excellent visualization of the aneurysm and the great vessels.

The ideal treatment of proximal and distal ligation of the main artery with excision or obliteration of the sac has been accomplished in three cases. The next procedure of value, which was employed in four cases, is ligation of the proximal artery (innominate) and distal arteries (subclavian and carotid) which is somewhat less hazardous to carry out. Of the seven patients, six were cured and one died eight years later, of recurrence and hemorrhage due to rupture.

There are several important points in the management of these cases: (1) in order to lessen the danger of a cerebral complication, repeated testing of the patient's ability to withstand prolonged carotid compression is valuable. (2) Although no incident of gangrene of the hand has been observed, the author noted that in his case temporary complete occlusion of the innominate artery resulted in a cold, pale, apparently bloodless hand. For that reason he partially occluded the innominate artery with a strip of fascia, and a band of cellophane was wrapped around the vessel. An upper thoracic sympathectomy was performed six weeks later which improved further the collateral circulation to the right hand. Because the bruit returned in full and the oscillometric reading in the right arm returned to a normal level, it was felt that the band around the artery had given way. Therefore, three and one-half months after the first procedure, Schumacker again opened the mediastinum and carried out proximal ligation of the innominate artery and distal ligation of the subclavian and common carotid arteries. The innominate, jugular, and subclavian veins were also ligated and excised. The aneurysmal sac was opened and the laminated thrombus was removed. The patient has remained entirely well for eighteen months with only slight fatigability and weakness of his right hand.

LORD.

Cooper, F. W., Jr., Robertson, R. L., and Dennis, E. W.: The Use of Tetraethylammonium Chloride in the Treatment of Experimental Acute Arterial Insufficiency. Surgery **22**:740 (Nov.), 1947.

The authors carried out resection of the distal aorta including the common iliac arteries and the deep circumflex iliac vessels in thirty dogs. In the control group of ten dogs, nine of the animals died within seven days of the operation. Autopsy showed that death was not due to hemorrhage or peritonitis. All of the animals experienced hindlimb paralysis, coldness, cyanosis, and varying degrees of swelling. In the group of twenty dogs treated with tetraethylammonium chloride, fourteen of the animals survived. These animals regained excellent functional activity within two to six days. Three of the six dogs which died had as their cause of death infection of a posterior extremity. One of the remaining animals died within twelve hours of the operation.

The tetraethylammonium chloride was administered intramuscularly, in doses of 25 mg. per kilogram of body weight immediately after excision of the arteries and was continued postoperatively at eight-hour intervals for three days.

The authors conclude that sympathetic interruption following an acute arterial injury is a valuable procedure and that tetraethylammonium chloride may be of value either as a substitute for other methods of sympathectic interruption or as a preliminary to them.

LORD.

Davis, H. A., and King, L. D.: A Comparative Study of Thromboangiitis Obliterans in White and Negro Patients. Surg., Gynec. & Obst. **85**:597 (Nov.), 1947.

The authors reviewed the literature with regard to the presence of thromboangiitis obliterans in the Negro race and pointed out that in only one of the ten reported cases could the patient be considered to be a full-blooded Negro. In their own series of sixty-four cases of thromboangiitis obliterans, nine were Negroes and in four of these pathologic examination verified the clinical diagnosis. However, it was established in at least one of them, a woman, that she was not a full-blooded Negro. With regard to the others, this point was evidently not investigated. The authors found that nonsurgical treatment was conspicuously less successful in Negro than in white patients.

ABRAMSON.

Gold, Harry, Kwit, N. T., Modell, W., Hanlon, L. W., Kramer, M., Greenberg, S., Otto, H. L., Cotlove, E. W., Benton, J. G., Pearlmutter, M., and Zahn, W.: A System for the Routine Treatment of the Failing Heart. Am. J. Med. **3**:665 (Dec.), 1947.

The authors propose a standardized regimen for the treatment of cardiac failure. It involves five cardinal factors: the simultaneous use of the mercurial diuretics, salt restriction, abundant water, digitoxin, and the charting of the course by a record of the body weight.

The patient is put at rest, given a diet consisting of four to six glasses of milk daily plus a water intake of two to three quarts. If no digitalis has been taken recently, 1.2 mg. of digitoxin are given at one time followed by 0.2 mg. daily as a maintenance dose. A daily weight record is kept. Mercuhydrin is given daily, beginning with a dose of .5 c.c. and increasing to as high as 2 c.c. daily. This regimen is continued until all signs of failure disappear and the weight declines to a resistant level, the "dry weight."

Maintenance is guided by the daily weight, and Mercuhydrin dosage determined accordingly. The patients or their families are taught to administer the latter. A more liberal diet is usually allowed but it is low in salt.

Each factor of the regimen is discussed in detail, as well as guides to treatment, maintenance programs, and unpleasant symptoms.

The authors state that the present study, comparing the results in 502 admissions for congestive failure with results in 140 similar admissions treated by the proposed system, shows that the symptoms and signs of congestive failure subside in about 90 per cent of hospital admissions when this system is employed routinely, against about 50 per cent with the current methods in common use; and that the duration of required hospital stay is reduced to about one-third of the time necessary

to bring about similar results by the current methods of treatment. They further state that only two types of results are obtained with the proposed method, namely, a few failures and the rest complete recoveries.

WOODS.

Friedman, M., and Bine, R., Jr.: Observations Concerning the Influence of Potassium Upon the Action of a Digitalis Glycoside (Lanatoside C). Am. J. M. Sc. **214**:633 (Dec.), 1947.

Although there is experimental and clinical evidence to support the theory that potassium in physiologic excess tends to inhibit the action of digitalis, there is little known about the physiologic inter-relationships of the two substances. This study, therefore, was concerned with the effects of different concentrations of potassium upon the normal embryonic duck heart. It was found that the absence of potassium led to arrhythmias and early cessation of beating. Excess potassium, conversely, depressed heart action. The absence of potassium was found to enhance the effects of a digitalis glycoside (lanatoside C), whereas an excess of potassium inhibited the actions of the same drug. Only large or toxic amounts of digitalis glycoside were found to cause a probable loss of potassium from the heart. Excess potassium was effective in inhibiting this process.

The results of the entire study indicated that excess potassium was able to inhibit the actions of digitalis glycoside (1) by depressing the irritability of the heart, and (2) by serving as a source of potassium to a heart apparently losing it after exposure to toxic amounts of digitalis.

DURANT.

Stepman, T. R., and Owyang, E.: Clinically Primary Tuberculous Pericarditis. Ann. Int. Med. **27**:914 (Dec.), 1947.

Three men, aged 60, 42, and 30 years, respectively, died following a protracted febrile illness during which a pericarditis with effusion was a prominent feature of the disease. In the first two patients, chronic pulmonary tuberculosis was not present and disseminated miliary tuberculosis was the terminal event. In the third patient, there were tuberculous excavative lesions in the lungs and a tuberculous enteritis with ascites. Pericardial paracentesis was performed in each patient during life, but in only one was the tubercle bacillus recovered from the pericardial fluid. At necropsy, a thickened adherent pericardium was noted in each instance.

WENDKOS.

LaDue, J. S., and Carter, S. B.: The Efficacy of Maintenance Doses of Digitalis in Preventing the Recurrence of Congestive Heart Failure. Ann. Int. Med. **27**:923 (Dec.), 1947.

One hundred four patients with heart disease associated with regular sinus rhythm who had been discharged from the hospital wards after treatment for congestive heart failure were followed at intervals of from one to four weeks over a period of from six months to two years. At the time the study was begun, most of the patients had been taking 0.1 to 0.3 Gm. of digitalis leaf per day for several weeks or months after discharge from the hospital. Measurements of venous pressure, circulation time, vital capacity, and weight were made during a one-to three-month period at intervals from one to four weeks; then digitalis was discontinued and the same measurements repeated at the same intervals of time. The degree of dyspnea, orthopnea, and edema was recorded, as well as the presence or absence of râles, the size of the liver, the cardiac findings, and the subjective state of the patient.

The data were broken down according to the variation in the measurements of the venous pressure, circulation time, vital capacity, weight, heart size, and frequency of the development of congestive heart failure while the patients were being studied. In general, it can be stated that none of the criteria employed for measurement of the circulation revealed any significant differences during the time digitalis was given to the patient and during the period that the drug was withheld. Patients with heart disease who were not in failure had on the average, lower vital capacity and longer circulation time measurements than did normal individuals of the same age

group. Changes in weight appeared to be just as sensitive as the level of the venous pressure, circulation time, or vital capacity in evaluation of the presence or approach of congestive heart failure. With the possible exception of changes in vital capacity and weight, detailed questioning of the patient with regard to dyspnea, orthopnea, and transient ankle edema, together with a careful physical examination, were more reliable in evaluating the state of the circulation than repeated measurements of the circulation time, venous pressure, or heart size.

It was noted that maintenance doses of digitalis leaf given to patients who had congestive heart failure failed to produce permanent and significant changes in diastolic heart volume once compensation was established. It was also observed that twice as many patients developed congestive heart failure during the period without digitalis than did those who were maintained on adequate doses of the drug.

Finally, the authors suggest that frequent re-evaluation of the therapeutic level of digitalization is indicated in patients who have at one time in the past developed congestive heart failure.

WENDKOS.

Tarr, L.: Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram of Man; A Study of the Changes Encountered in 141 Patients Treated for Schistosomiasis. Ann. Int. Med. **27**:970 (Dec.) 1947.

Serial electrocardiograms were made in 141 patients who were treated with Fuadin and/or tarter emetic because of infestation with *Schistosoma japonicum*. Every patient receiving a course of tarter emetic showed some degree of T-wave alteration in the electrocardiogram, varying from slight depression to deep inversion, whereas in those receiving Fuadin, comparable alterations occurred in 57 to 80 per cent of the patients. In 30 per cent of the entire number, the magnitude of the abnormality was of a high order, whereas only 6 to 14 per cent of the Fuadin-treated group showed such marked changes. In none of these patients did associated S-T segment deviations occur. Although the quantitative change in the electrocardiogram in the tarter emetic and Fuadin-treated groups was different, qualitatively, the alterations encountered were identical. A striking feature was the reversible nature of the changes. In 90 per cent of those whose electrocardiograms showed varying degrees of T-wave change following either small or large doses of Fuadin or tartar emetic, these deflections returned to normal in thirty to sixty days after cessation of treatments. No correlation should be established between the amount of the drug which had been administered and the degree of T-wave change which developed.

Fuadin is a sodium compound of trivalent antimony and tartar emetic is a potassium compound of trivalent antimony. Since the electrocardiographic changes following potassium administration are entirely different from those observed, and since the alterations following the administration of these two drugs were similar, the potassium ion was not considered a possible factor responsible for the modification of the T wave. A vagal origin was seemingly excluded because the abnormalities were not influenced by atropine sulfate. However, the amount of atropine sulfate which was used was inadequate to permit any valid conclusion in this regard. The author considers that the T-wave alterations are the result of a temporary deposition of antimony in the heart muscle which, in turn, alters the electrical activity of the ventricle. The disappearance of the T-wave changes, therefore, is considered to be the result of excretions of this metal from the heart muscle.

WENDKOS.

Gibson, J. G., II, Seligman, A. M., Peacock, W. C., Fine, J., Aub, J. C., and Evans, R. D.: The Circulating Red and Plasma Volume and the Distribution of Blood in Large and Minute Vessels in Experimental Shock in Dogs, Measured by Radioactive Isotopes of Iron and Iodine. J. Clin. Investigation **26**:126 (Jan.), 1947.

Normal dogs under morphine narcosis or Nembutal anesthesia were subjected to a variety of procedures designed to induce various degrees of shock. Measurement of the circulating blood volume in animals shocked by hemorrhage revealed a greater reduction in the volume of circulating cells and plasma than could be accounted for by known *external* blood loss. By special techniques

it was found that this discrepancy was due to *trapping* of blood within the minute vessels of all the organs in the body and further, that the erythrocytes removed from the *effective* circulation within the minute vessels represented a very large percentage of the total quantity of erythrocytes normally circulating within these vessels. This phenomenon of trapping was observed regardless of the nature of the shocking procedure, e.g., burns, muscle trauma, hemorrhage, or administration of bacterial toxins.

Although the degree of trapping bore no relationship to percentile reduction in total blood volume, it did appear to be roughly related to the decline in arterial pressure, in that the ratio of circulating to total red cells in minute vessels was 0.8 or less in dogs whose mean arterial pressures fell more than 65 mm. Hg, whereas ratios higher than 0.8 were accompanied by pressure drops of less than 30 mm. of mercury.

In one series of experiments, infusions of bovine albumin were given and resulted in an immediate rise in mean arterial pressure in most shocked animals. Infused animals in which the circulating red cell volume displayed no upward trend had only a temporary rise in arterial pressure and eventually succumbed; others in which the circulating red cell volume increased following infusion maintained their arterial pressures and survived.

These experiments indicate that the treatment of shock should be directed not only toward the restoration of blood volume but also toward *circulating* red cell volume in order that trapped erythrocytes be flushed back into the circulation.

FRIEDLAND.

Houston, C. S., and Riley, R. L.: Respiratory and Circulatory Changes During Acclimatization To High Altitude. Am. J. Physiol. 149:565 (June), 1947.

Detailed studies of the respiratory and circulatory changes which occur during the process of acclimatization to oxygen lack were made on four men exposed to gradually increasing simulated altitude during one month in a low pressure chamber. The data strengthen the concept that acclimatization consists of a series of integrated adaptations which tend to restore the oxygen pressure of the tissues toward normal sea level values despite the lowered pO_2 of the atmosphere.

The same pulmonary and circulatory changes which caused an increase in pO_2 as acclimatization progress necessarily caused a decrease in pCO_2; and an initial effect of the decrease in pCO_2 was an increase in the alkalinity of the blood. As acclimatization progressed, further changes occurred to counteract this respiratory alkalosis. The fall in blood bicarbonate reflected the extent of these changes which included a net increase in the other negative ions and probably a net decrease in the positive ions.

There is no evidence that cellular metabolism decreased as part of the acclimatization process, since the oxygen consumption remained the same at simulated high altitude as at sea level, both during rest and work. Since clinical evidence indicated that the subjects were moderately anoxic, it appears that cellular function was impaired by low pO_2 even though the amount of oxygen used by the cells remained normal.

BERNSTEIN.

Altschule, M. D., and Rosenfeld, F. M.: Increased Catabolism Following Acute Myocardial Infarction. Arch. Int. Med. 80:74 (July), 1947.

Three patients with myocardial infarction in whom persistent shock did not occur were studied and they all showed evidences of a preponderance of catabolic activity. The daily nitrogen loss averaged 4.4 to 8.1 Gm. per day as compared with an average daily loss of 0.38 to 0.58 Gm. per day in a control group. The authors presume the rise in nonprotein nitrogen which frequently occurs following myocardial infarction is probably the result of increased delivery of nitrogen to the kidneys consequent to increased protein catabolism at a time when renal function may be decreased as a consequence of vasoconstriction or, in some cases, shock. The elevation of blood lactate and pyruvate are also probably a consequence of increased destruction of body protein and increased catabolism in general. Myocardial infarction is compared to severe thyrotoxicosis, thermal burns,

and prolonged high artificial fevers as being characterized by a negative nitrogen balance, hyperglycemia, elevated blood lactate and pyruvate, and not infrequently, an unexplained hyperbilirubinemia.

BERNSTEIN.

Rosenkrantz, J. A., and Marshal, C.: Basal Metabolic Rate in Hypertensive Vascular Disease. Arch. Int. Med. **80**:81 (July), 1947.

In hypertensive vascular disease without cardiac insufficiency (determined by checking the electrocardiogram 6-foot silhouette, and the physical condition), a significant incidence of hypermetabolism has been demonstrated, in that there is a decided positive correlation between basal metabolic rate and both systolic and diastolic blood pressure. On the other hand, there appears to be no significant association between basal heat production and pulse pressure. Further analysis revealed a greater incidence of renal dysfunction in hypertensive patients with increased basal metabolic rates than in those with normal or subnormal basal heat production, perhaps because of the fact that those with renal dysfunction had a greater elevation in blood pressure. The possibility that thoracolumbar sympathectomy can lower basal metabolic rates may explain one of the mechanisms producing elevated rates in some hypertensive patients. In this study, thoracolumbar sympathectomy resulted in a reduction of basal heat production without an appreciable alteration of blood pressure. One must consider that cardiac work may be a factor in elevating metabolic rate since a direct correlation between basal metabolic rates and blood pressure, as well as a greater incidence of renal dysfunction was found in this series of hypertensive patients with elevated metabolic rates.

BERNSTEIN.

Stead, E. A., Jr., and Warren, J. V.: Cardiac Output in Man. Arch. Int. Med. **80**:237 (Aug.), 1947.

This paper attempts to present new data in an effort to throw light on the mechanisms controlling the cardiac output in man, a subject which current medical teaching admits is based mainly on the concepts of animal physiology. The cardiac output was determined by the direct Fick principle or the ballistocardiograph. It was found that the ventricles play an active rather than a passive role in determining the cardiac output, in that the cardiac output is varied by changes in ventricular relaxation and contraction which are independent of fairly wide variations in atrial pressure. Lowering the arterial pressure causes an abrupt rise in cardiac output which occurs too rapidly for a humoral mechanism. Anxiety and exercise increase output even in the presence of an increase in arterial pressure.

It is suggested that reflex stimulation of ventricular activity accounts for the changes in cardiac output during daily activity and the afferent stimuli may arise in part from a lowering of the arterial pressure, movement of limbs during exercise, and the emotional content of thought Clinical observations which support the concept that the cardiac output is under reflex control are discussed.

BERNSTEIN.

Smith, J. A., and Levine, S. A.: Aortic Stenosis With Elevated Metabolic Rate Simulating Hyperthyroidism. Arch. Int. Med. **80**:265 (Aug.), 1947.

The authors report a series of four cases of aortic stenosis without dyspnea or significant pulmonary congestion in which the patients showed definite and persistent elevated basal metabolic rates (34 to 53 per cent) and had normal thyroid glands grossly and microscopically. In view of the fact that these patients also manifested some other feature suggestive of thyrotoxicosis, the authors suggest that we add this group of patients to the group of conditions that need to be considered in the differential diagnosis of masked thyrocardiac disease; that is, cardiac failure, hypertension, per se, polycythemia, coarctation of the aorta, and cardiac failure associated with beriberi.

BERNSTEIN.

Book Reviews

VARICES SU TRATAMIENTO BASADO EN LA FLEBOGRAFIA. By Dr. F. Martorell, Barcelona, Spain, 1946, Teleres Groficas Ibero-Americanos, 140 pages, 118 figures.

This book by Dr. F. Martorell, Chief of the Vascular Surgery Division of the Polyclinic Institute of Barcelona, is an exhaustive attempt at a precise diagnosis of the varicosities of the lower extremities by phlebography. The author devotes two chapters to the elemental facts of the venous circulation in the lower extremities. The differential diagnosis of varices is contained in the second part of the book. The Trendelenburg phenomenon, Perthes, Ochsner and Mahorner, and Pratt tests are discussed and compared with the author's own method. The other methods are too inexact, and this is the reason why Dr. Martorell has developed phlebograms to such a high degree of efficiency. An exact visualization of the insufficient communicating veins gives the localization for ligation, shortens the operation, avoids useless and dangerous ligations, and permits ambulatory treatment of all patients, thus minimizing the chance of embolization. The book is amply illustrated with diagrams and photographs. It deserves study in the English speaking medical world.

BERNARD E. NUNEZ, M.D.

TENSION ARTERIAL Y BIOTIPO. By F. Schaposnik, Buenos Aires, 1947, El Ateneo, 120 pages, 27 charts.

The author studied the possible correlation between arterial blood pressure and physical constitution. Seven hundred nine persons of both sexes between 14 and 22 years of age were studied.

The macrosplanchnic type showed the greatest percentage of readings above 140 mm. Hg systolic, while the normosphlanchnic type presented such readings more often than the microsplanchnic. Tall persons usually have a higher blood pressure than persons of average height, but smaller individuals may also have higher than normal figures.

The microsplanchnic type presents a lower diastolic pressure than the normal type while the macrosplanchnic type presents a higher diastolic pressure than the normal.

Pulse pressure was larger in macrosplanchnic men and in normal women than in the other types.

In conclusion, a definite relationship between body structure and blood pressure is suggested, even if the difference between the observed figures is not striking.

A. LUISADA, M.D.

DERIVACÕES UNIPOLARES DAS EXTREMIDADES CONTRIBUICÃO AO ESTUDO DOS SEUS ASPECTOS NORMAIS. By Horácio Kneese de Melo, Sao Paulo, 1947, Indústria Grafica Siqueria, 78 pages and 15 figures.

This seventy-eight page monograph by Dr. Horácio Kneese de Melo of Brazil is an interesting presentation of the normal variations of augmented unipolar extremity leads. In Chapter I, he discusses the advantages of unipolar leads in general. In Chapter II, he describes Goldberger's modification of Wilson's central terminal, which he uses. He states that he found that the augmented unipolar extremity leads taken with or without the resistors are identical. In Chapter III, he reviews Wilson's description of the electrical positions of the heart, which he employs, and he describes a variation of the Einthoven triangle for use with unipolar extremity leads.

The remaining five chapters describe his observations of the aV leads in 221 normal subjects, including newborn infants and children. His observations on the T wave are especially interest-

ing. He found an upward T in Lead aV_R in several of his newborn subjects. This has not been previously noted. In the aV_L lead a downward T with a tall R occurred in only one adult. In the aV_F lead, a downward T with a tall R was common in children and adolescents.

The monograph is written in Portuguese in a simple and easy style. It is well printed and the illustrations are clear.

EMANUEL GOLDBERGER, M.D.

FISIOPATOLOGIA DELLA CIRCOLAZIONE VENOSA. By L. Condorelli, Corso, Italy, 1946, Azienda Poligrafica Editoriale, 336 pages and 83 tracings, 1200 lire.

This book is a monographic study of the venous circulation. Most of the material presented has already been published by the author and his pupils. After describing a new apparatus for continuous recording of venous pressure in man, the author applies the results of the method to the interpretation of various circulatory conditions.

While much of the present physiologic knowledge concerning venous circulation is ignored, some new conceptions are advanced. Some of these, such as that concerning venous hypertonus (so-called "active" venous hypertension), are attractive but do not seem to be substantiated by solid evidence. Bibliographic quotations are chiefly limited to French and German work of the last ten years.

The author presents a large material with undeniable skill, but the style and composition of the book are far from being clear.

A. LUISADA, M.D.

TEMPI DI CIRCOLO E VELOCITÀ DISTRETTUALE DI CORRENTE. By A. Francaviglia and A. Turchetti, Catania, 1946, Azienda Poligrafica Editoriale, 254 pages and 36 figures, price: 680 lire.

This book deals with circulation time and circulation speed with special regard to the rate of circulation in limited sections of the cardiovascular system. After a review of the different methods for measuring circulation time, the authors state the reasons for choosing sodium dehydrocholate. Using this drug, circulation rate is studied in normal subjects before and after the administration of drugs, exertion, compression of the eyeballs, apnea or forced respiration, and introduction of air in the course of therapeutic pneumothorax. It is further studied in cardiac patients before and after exertion, and in hypertensive and hypotensive patients. In a later chapter, circulation time and speed are measured in limited sections of the cardiovascular system.

While a great deal of data has been collected, some of them of interest, their evaluation is by no means easy. This is due to the failure of the author to clearly separate personal observation from the observations of others, poor distribution of the subject, and the failure to clearly summarize the results and conclusions of the study.

A. LUISADA, M.D.

A DOENCA DE CHAGAS NA BAHIA. By Prof. Adriano de Azevedo Ponde', Bahia, 1947, Imprensa Vitoria, 126 pages and 107 figures.

Chagas' disease is South American trypanosomiasis. It differs from the African sleeping sickness in its clinical manifestations. It has an acute and a chronic form. In the chronic form, nervous system or cardiovascular symptoms predominate. Several descriptions of the cardiac aspects of Chagas' disease are found in the South American literature and a short description may be found in White's "Heart Disease." Most cases occur in Brazil, and on the basis of thirty-seven cases, this monograph presents the clinical picture which is quite different from anything cardiologists ever see in this country.

Patients acquire the disease by sleeping in dwellings infested with *Triatoma magista*, a bug which carries the *Trypanosoma cruzi* and sucks the blood of its victims at night. The *Trypanosoma* seeks with preference the myocardium where it sometimes may be found, post mortem, imbedded within the myocardial fibers.

The clinical picture which it produces is one of congestive failure which persists for months or years, proves resistant to treatment except for temporary remissions, and finally ends in death from asystole.

Of thirty-six cases of chronic Chagas' disease, thirty were between 11 and 40 years, seventeen between 21 and 30 years of age. Thus, it is a disease of young adults. The symptoms were palpitation, dyspnea, and various precordial pains of rather indefinite nature. As congestive failure developed, enlargement of the liver and dependent edema (right-sided failure) predominated, signs of left-sided failure being much less marked. Cardiac enlargement was frequent but varied greatly in degree. Valvular involvement was no part of the picture, though systolic murmurs might arise from relative mitral insufficiency.

Most extraordinary, however, were the electrocardiographic findings: this disease causes extensive damage to impulse formation, the conduction system, and the myocardium. All kinds of ectopic origins of complexes are seen both in auricles and ventricles. Auriculoventricular block is more common in this form of heart disease than in any other, eleven of the thirty-six cases of chronic Chagas' disease had complete A-V dissociation, and six others had incomplete A-V block. Another peculiarity is the frequency of right bundle branch block. Typical and persistent left bundle branch block was not seen in this series. No satisfactory explanation is given for this predominance of right ventricular pathology and failure. Another unusual feature was the changes which the electrocardiographic alterations underwent, especially in the S-T and T segments when serial tracings were taken.

Altogether, Chagas' disease of the heart, as described by this able cardiologist, presents an intriguing and interesting picture, quite novel to the more or less standardized patterns to which we have become accustomed.

Anyone who wishes to read this book will do well to orient himself by first reading a chapter in a textbook on tropical diseases such as the textbook by Bercovitz. The case reports are full and complete, occupying pages 14 to 87. Then follows an analysis of the material, a discussion which contains the essence of the subject, and finally an abstract in English which becomes a little clearer if one has first mastered the Portuguese text. The references appear to be adequate and ample.

JULIUS JENSEN, M.D.

SEMEIOLOGIA CARDIOVASCULAR. By R. Carral y de Teresa, México, 1947, Instituto Nacional de Cardiologia, 500 pages and 93 figures.

This book is devoted to "Cardiovascular Semeiology." The first part deals with functional semeiology, including a study of dyspnea, cyanosis, precordial pain, and cerebral symptoms. The second part deals with hemodynamics. The mechanisms of cardiac failure, venous hypertension, serous effusions, cardiac output, circulation speed, and blood pressure are discussed, with separate chapters for hypertension and hypotension. In the third part, physical examination is described with special emphasis on auscultation. The mechanism of production of murmurs and phonocardiography is discussed in detail. The last three parts are respectively devoted to various laboratory methods, roentgenology, and electrocardiography.

The book contains a rich and well-organized collection of data which make its reading interesting and easy. The quotations from the literature are well chosen and those from the works of Mexican authors are particularly interesting and useful.

While illustrations of methods of physical examination would have increased the value of the book for beginners, the roentgenologic, stethographic, and electrocardiographic tracings are clear and, at times, particularly interesting. The main fault of the book is that it represents a compromise between the stated purpose of the author (semeiology) and the unexpressed wish of writing a book on cardiology. If the title is correct, repeated description of clinical entities, including pathology, and detailed discussion of therapeutic procedures are superfluous. In a book on cardiology, the order of the chapters should be different and the space devoted to description of symptoms and signs should be more proportionate to the total volume. Inclusion of chapters devoted to peripheral circulation would increase the value of the book. The same can be said of an index of subjects.

A. LUISADA, M.D.

CORNELL CONFERENCE ON THERAPY, VOL. II. Edited by Harry Gold, M.D., David P. Barr, M.D., McKeen Cattell, M.D., Eugene F. Du Bois, M.D., Paul A. Bunn, M.D., and Walter Modell, M.D. New York, 1947, The Macmillan Company, 354 pages, price $3.75.

The Editorial Board for this publication has apparently fulfilled its stated purposes, namely, to explore some aspects of special interest in pharmacology and therapeutics, to analyze the evidence on controversial points of opinion and practice and break down the physiologic and pharmacologic bases of therapeutic measures, and to present these on the level of the general practitioner. These conferences assemble many practical therapeutic facts, and in spite of the disclaim of the editors of such an objective, the book will serve as a reference source. As such it would have been more valuable if more of a bibliography were included, especially where space prevents presentation of precise techniques. Likewise, an index would be helpful.

The discussion and question method of teaching, which is so stimulating to the individual present at a conference, at times confuses a reader of such material presented in publication. This results not only from certain verbosity, but also from conflicting opinions, especially relevant to the value of new procedures or material. From the teaching standpoint it would seem wiser either to present the most authoritative discussion, or else have the moderator more forcibly discredit probably erroneous opinions.

The presence of personal bias is apparent in the dominant opinion on certain subjects, especially the Sister Kenny treatment of poliomyelitis, the inadequacy of xanthines as diuretics, and the entire subject of quinidine therapy. The opinions expressed on the use of quinidine may be popular at present, but are not uniformly accepted by many excellent cardiologists. It is most notably illustrated on the views that quinidine must not be used with, or presumably shortly after, digitalis; it should not be used in myocardial infarction, presumably 0.2 Gm., three to four times daily as prophylactic doses, because "it depresses the myocardium too much for its use"; it rarely, if ever, should be used in conversion of permanent auricular fibrillation, overlooking the increased incidence of embolic phenomena, an opinion disputed by Dr. Pardee; it is rapidly eliminated; and that after conversion of an arrhythmia, the maintenance dose is rarely used.

Certain chapters are especially excellent reviews of the subjects considered, especially "Sympathomimetic Amines," "Edema and Dehydration," and "Rheumatic Fever." The unanswered question often indicates where investigation should be pursued, and the mode of presentation illuminates, but occasionally not as well as it should, the difference between accurate clinical observation, applied experimental data, and opinion colored by various causes of personal bias. The occasional human weaknesses shown by such an excellent group so seriously at work to avoid them is a good moral lesson to the reader in guarding the formation of his own therapeutic judgments.

JOHN J. SAMPSON, M.D.

UNIPOLAR LEAD ELECTROCARDIOGRAPHY. By Emanuel Goldberger, M.D. Philadelphia, 1947, Lea & Febiger, 82 pages and 88 figures. Price $4.00.

This monograph describes and analyzes electrocardiographic patterns primarily in terms of unipolar leads. It is pointed out that such leads provide a recording of potentials which are not significantly affected by the indifferent electrode, and therefore can be explained in terms of simple, fundamental principles. The material presented is based on a seven-year study of these leads by the author, the study having had its origin in an investigation of the Q wave by means of Wilson leads, followed by the modification of these leads to form the augmented unipolar leads of the author.

The subject is introduced by a brief discussion of the basic principles of electrocardiography. The validity of the Einthoven triangle theory is accepted on the basis of experimental data previously published by the author and by others. The various methods of taking unipolar leads are described, including both the author's method and the use of the Wilson central terminal. Many will disagree with the advisability of omitting the 5000 ohm resistances in the former. The discussion of the relationships between the standard leads and unipolar extremity leads and between ordinary precordial leads and unipolar precordial leads is entirely adequate. Following this, the major portion of the volume is devoted to the normal electrocardiogram, to the effects

of position of the heart upon the normal electrocardiogram, and to abnormal electrocardiograms, including those associated with hypertrophy of the various chambers, bundle branch block, myocardial injury, and digitalis administration. Proper stress is placed upon the value of unipolar electrocardiography in the interpretation of many cardiac conditions in which standard electrocardiographic methods are entirely inadequate, among which might be mentioned especially the value of the left leg potentials in the interpretation of the significance of a Q wave in Lead III. No attempt is made to discuss the arrhythmias, since unipolar electrocardiography contributes nothing to their diagnosis except in cases of nodal rhythm.

Throughout the volume, tremendous stress is placed upon the effect of changes in the position of the heart through rotation upon any one of its three axes, or upon a combination of these axes. The theorizing along this line is extended to a degree which will not be acceptable to most. Corresponding radiologic descriptions of all of the positional electrocardiographic patterns are omitted, "partly because much of this information is still incomplete." Nowhere in the volume is there found the caution with regard to this subject expressed by Wilson and his co-workers in this statement, "The names given to these positions are not intended to imply that the electrocardiographic position of the heart is uniquely determined by its anatomic position, either when this organ is normal or abnormal. We are not only aware, but are also certain, that a change in the one is not necessarily accompanied by a change in the other." This warning is especially indicated when there is a localized lesion of the myocardium, and yet the positional theories are carried over without apology into the subject of myocardial infarction, and the statement is made that the heart usually lies horizontally after anterior infarction and vertically after posterior infarction. It is explained that the rotation is due to factors differing from those that affect the position of the normal or hypertrophied heart, and that the abnormal contraction of the involved portion of the myocardium, together with the force of contraction of the remaining normal muscle or in some cases localized dilatations of the wall, may be responsible for the abnormal rotation. This will be extremely difficult for many to accept without the presentation of a great deal more evidence.

In the preface the statement is made that "standard leads and unipolar extremity leads are somewhat different from the other leads because they not only depend on the basic unipolar lead patterns, but they vary greatly with changes in the position of the heart." This would seem to imply that precordial leads are not influenced by changes in the position of the heart, though this is at variance with the remainder of the text and with common experience. No attempt is made at any point in the description of precordial leads to discuss or even mention the important transitional zone and the facts that are known concerning its variability in the normal. The impression is very definitely given that the entire left ventricle gives qR or qRS patterns in unipolar leads that face its epicardial surface. This is not in accord either with experimental work with direct leads in the animal or with studies of the transitional zone in the human, since the anterior surface of the left ventricle gives rise to RS patterns, and only the lateral and posterobasal portions demonstrate an initial negative deflection in the normal heart.

Because of these objections and other less important ones, such as obscure phraseology in many places, this book cannot be recommended for one who does not have a good, basic knowledge of electrocardiography. It does contain, however, much valuable information, such as the criteria for the abnormality of the Q waves.

THOMAS M. DURANT M.D.

A PRIMER OF CARDIOLOGY. By George E. Burch, M.D., F.A.C.P., and Paul Reaser, M.D. Philadelphia, 1947, Lea & Febiger, 272 pages and 203 figures. Price $4.50.

A Primer of Cardiology is just what the authors state it to be; a primer designed for medical students and practitioners to serve as an introduction to more serious study. As such it can be recommended. For the medical student, the authors' attempts to correlate the basic sciences of physiology, physics, and physical chemistry with clinical phenomena should be very helpful. For example, the section on heart sounds is particularly good. The correlation of phonocardiographic records with other events in the heart cycle is well done and the diagrams are very instructive. The analysis of the phenomena associated with split heart sounds and gallop rhythm is particularly good. The presentation is difficult to follow, however, because the text is so abbreviated.

There are several points throughout the book with which this reviewer does not agree. For instance, it is stated that the Graham Steell murmur indicating pulmonary insufficiency is common. The authors define heart disease as any disturbance in cardiac function that disturbs the patient in any way. This I believe to be much too broad; a concept that would make the handling of the cardiac neuroses more difficult. Under heart disease due to the aging process, the authors include arteriosclerosis of the coronary arteries. The experience with our troops, in which, I am told 1,000 young men from the ages of 18 to 40 years died of cardiac infarction, casts doubt upon the concept of this disease as an aging phenomenon. The section on cardiovascular syphilis is, in the reviewer's opinion, the poorest in the book. It contains a section on acute aortitis in which dyspnea and vague substernal pain are listed as symptoms. Aortitis is a symptomless disease. In the section on diagnosis, it is stated that aortitis is easily diagnosed and that it appears clinically after only several weeks of infection. This is certainly not the prevailing opinion. The authors are also oversanguine when they state that syphilitic aortitis will respond to therapy with complete cure if early and adequate antisyphilitic therapy is administered.

These criticisms are presented in a spirit of helpfulness and in the hope that some of them may be accepted for the next edition.

There are many very good clinical sections; the critique of our knowledge of congestive heart failure, the presentation of cardiac infarction, angina pectoris, and hypertensive heart disease. It is pleasing to see that the authors use the term diastolic hypertension.

Having read the book, this reviewer is left with the feeling that it will serve a useful purpose but that it would be more enthusiastically recommended if some of the statements enumerated could be corrected.

EDWIN P. MAYNARD, JR., M. D.

CONGENITAL MALFORMATIONS OF THE HEART. By Helen B. Taussig, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, and Director of the Children's Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital, New York, N. Y., 1947, The Commonwealth Fund, 1618 pages, 46 plates in color, 177 other illustrations. Price $10.

Contents: Foreword by Edwards A. Park, M.D.

Part One. Physiology of the Malformed Heart and Diagnostic Principles

I. Embryology, Etiology, Basic Principles of Analysis, and Fetal Circulation
II. Methods of Diagnosis
III. Cyanosis

Part Two. Malformations Which Deprive the Body of an Adequate Amount of Oxygenated Blood

IV. Defective Development of the Right Ventricle and Tricuspid Atresia
V. The Tetralogy of Fallot
VI. Pulmonary Stenosis or Atresia and Extreme Dextroposition of the Aorta
VII. Pure Pulmonary Stenosis
VIII. Aortic Atresia and Marked Hypoplasia of the Aortic Orifice
IX. Absence of the Aortic Arch
X. Complete Transposition of the Great Vessels and the Common Associated Anomalies
XI. Truncus Arteriosus
XII. A Single Ventricle and a Rudimentary Outlet Chamber
XIII. Anomalies of the Venous Return
XIV. The Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery

Part Three. Malformations Which Permit the Body to Receive an Oxygen Supply Sufficient for the Growth of the Individual

XV. Persistent Patency of the Ductus Arteriosus
XVI. Defects in the Auricular Septum
XVII. Defects in the Ventricular Septum

XVIII. The Eisenmenger Complex
XIX. Aneurysm in the Sinus of Valsalva With Rupture Into the Right Ventricle
XX. Anomalies of the Aortic Valve and of the Ascending Aorta
XXI. Anomalies of the Aortic Arch
XXII. Coarctation of the Aorta
XXIII. Dextrocardia With or Without Situs Inversus
XXIV. Ebstein's Disease
XXV. Complete Heart Block and Other Cardiac Arrhythmias

Part Four. Therapeutic Measures

XXVI. General Medical Care
XXVII. Medical Aspects of the Surgical Correction of Congenital Pulmonary Stenosis or Atresia

Correlation of the Salient Features Aiding in Diagnosis

Index

Helen Taussig's new book on congenital heart disease is a milestone in both the development and the distribution of our knowledge about the heart. She has done important pioneering herself and has presented in some detail these contributions of her own. Also, she has covered in a clear and concise form a good deal that is known about congential heart disease that has come from other sources. However, one would have liked to have had included in this book more of the new work that has been going on in the physiologic study of congenital defects of the heart; in particular, by cardiac catheterization. Events move so rapidly that there has come new information within the last year or so that was not included in this book; for example, the current availability of the determination of pulmonary blood pressure by cardiac catheterization, doing away with our guesswork of former days and with the need of waiting until actual operation before measuring the pulmonary blood pressure. There is also inadequate recognition of the increasing success of penicillin therapy in the treatment of subacute bacterial endocarditis as a complication and the displacement of sulfonamide therapy by penicillin. Similarly, one would like to see in future editions x-ray pictures of Diodrast injections to reinforce the excellent diagrams that appear throughout the book.

Some readers may complain of the lack of long discussions about embryology, but this book is avowedly a clinical treatise and contains, in the opinion of the reviewer, an adequate amount of reference to the fetal development of the heart itself.

The author's pioneer contributions have been largely in the field of the cyanotic types of congenital heart disease and are particularly presented in Chapter IV (Defective Development of the Right Ventricle and Tricuspid Atresia), Chapter V (The Tetralogy of Fallot, in the remarkable surgical treatment of which Taussig's name is forever emblazoned along with that of Blalock), Chapter X (Complete Transposition of the Great Vessels and the Common Associated Anomalies), and Chapter XIII (Anomalies of the Venous Return). Also in Chapter XXI (Anomalies of the Aortic Arch) in Part Three, which concerns the noncyanotic types of heart disease, Taussig has presented an unusually helpful discussion based on a good deal of her own studies of congenital heart disease.

The reviewer on reading through this volume has noted down in particular several statements that deserve more emphasis than has sometimes been accorded. A few examples follow herewith.

On page 15 she states: "All the present experimental evidence indicates that although anatomical closure of the ductus arteriosus may not be completed for two months, functional closure of the ductus arteriosus occurs shortly after birth."

On page 18, there is a sentence which is important for the internist to remember, namely that "The infant's heart is larger in proportion to the chest than is that of the adult" and on page 24 there is the observation that "in the infant the chest is wider than it is long, in the child approximately as long as it is wide, and in the adult longer than it is wide" and that "in infancy the difference in pressure between the two circulations is slight; with variations in the systemic and pulmonary pressure, murmurs come and go. Therefore, too great emphasis should not be placed on murmurs."

On page 20 we find "A reduplication of the second sound is clear evidence of the existence of both great vessels" and on page 22 "cyanosis always precedes clubbing of the extremities; indeed clubbing of the extremities, although a characteristic finding in older patients, is seldom seen in early infancy." In referring to râles in the lungs due to pulmonary congestion, not infection, the author writes that since most malformations which cause persistent cyanosis are associated with marked diminution in the flow of blood to the lungs, "therefore, cyanosis accompanied by râles indicates a malformation which permits adequate circulation to the lungs."

On page 48 we find "The P waves give some information concerning the size of the auricles. Abnormally high pointed P waves occur with great enlargement of the right auricle. Notching and prolongation of the P waves are seen with enlargement of the left auricle."

On page 54 there is the statement "Most infants in whom cyanosis is due primarily to a large venous-arterial shunt and to the failure of the blood to reach the lungs for oxygenation die at an early age. For this reason secondary changes in the lungs become of increasing importance in the older age groups. These pulmonary factors become so pronounced in adults that many internists believe that they are of far greater importance than is the reduction in the pulmonary circulation," especially in the case of the Eisenmenger complex in which there is evidence of pulmonary or endarterial change.

One could continue to quote many other interesting and instructive passages through the book which it would be well for both the internist and cardiologist, per se, to read carefully. Such passages appear right to the end of the whole book. Near the end, for example, on page 550 there is the following interesting advice: "Broadly speaking, if the cardiothoracic ratio is 55 per cent or under, a child with a congenital malformation of the heart does not need digitalis. With a cardiothoracic ratio of 55 to 64 per cent he may or may not need digitalis; with a cardiothoracic ratio of 65 per cent or over, compensation can seldom be maintained without the aid of digitalis."

The reviewer would like to emphasize particularly the excellence of the plates of which there are forty-six in color; with their legends they would make a very good atlas, per se. Plate 35, however, is a bit unsatisfactory and could be improved to make it clearer. The other illustrations also are good; they include line drawings, teleroentgenograms, electrocardiograms, and a few other subjects. At the end of the book there is a tabular appendix, a useful summary of the clinical findings. There is also a very adequate index of thirty-six pages.

The author has emphasized the preponderant importance of x-ray study in the diagnosis of the individual congenital defects, but much experience and skill is needed to follow that lead. The left anterior oblique position, both for roentgenograms and fluoroscopy, is constantly referred to as of the greatest value in determining the relative sizes of the heart chambers. Doubtless there are difficulties involved, as for example, when the heart is so large that it may be impossible to tell whether both chambers are enlarged or whether one or the other is so much enlarged that it displaces the other anteriorly or posteriorly. The value of electrocardiography is perhaps somewhat greater than considered in this book, for, on occasion, as in the case of tricuspid atresia, it is possibly the most important or most rapid clue to the diagnosis.

The more adverse criticisms of the reviewer concern, in the first place, the incompleteness of the book with respect to such a subject as cardiac catheterization which, he thinks, might well be included in the next edition, and second, considerable repetition, particularly with reference to chapter summaries. A good many pages are taken up with chapter summaries, the time for the reading of which could be better devoted to a rereading of the chapter itself; for example, Chapter XXVII with 19 pages has three devoted entirely to the summary. Since the plates also give quite satisfactory summaries of each condition, the chapter summaries might well be omitted with the saving of many pages.

There are surprisingly few errors of spelling or construction and also very few omissions of important matter. A comment might have been well added about the possible strain on the heart (to be watched with interest in the future) which may result from the Blalock-Taussig operation in which the shunt, somewhat like that of a ductus arteriosus, is artificially produced.

In conclusion, this book by an expert specialist can be highly recommended to serve both as a textbook to read, per se, and for reference after that for cardiologists, general internists, general practitioners, and medical students alike.

P. D. White, M.D.

American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.

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NEW HEADQUARTERS FOR AMERICAN HEART ASSOCIATION

The American Heart Association has moved its offices from 1790 Broadway to 1775 Broadway, New York 19, N. Y. The new telephone number is Plaza 7-2045.

SCIENTIFIC COUNCIL

A list of more than 700 names to comprise the Founder's Group of the Scientific Council has been approved by the Board of Directors. Membership in the Council is granted on the basis of training and scientific contributions to the field of cardiovascular disease. It is a requirement that all members of the Scientific Council shall be or become members of the Association.

The first meeting of the Scientific Council will be held in Chicago in June, 1948, at the time of the Annual Scientific Sessions.

PROCEEDINGS FOR THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

These proceedings appeared in the May issue of the American Heart Journal. In order that they appear at the earliest possible moment, an explanation of their inclusion in the Journal had to be omitted. The American Heart Association, the editors, and the publishers now wish to express their appreciation to the American Society for the Study of Arteriosclerosis for the privilege of presenting these proceedings.

THE GEORGE BROWN MEMORIAL LECTURE

In the announced program of the Twenty-first Scientific Session of the American Heart Association, it was stated that the George Brown Memorial Lecture would be given by Dr. Edgar V. Allen. Unfortunately, Dr. Allen will be unable to give the lecture because of illness. Dr. Irvine H. Page of Cleveland, Ohio, has consented to take Dr. Allen's place. The title of Dr. Page's lecture is "On the Nature and Treatment of Shock."

FINANCE COMMITTEE

Formation of a Finance Committee consisting of Mr. Alfred C. Howell, Bethel, Conn.; Mr. Robert L. Mehornay, Kansas City, Mo.; Mr. S. DeWitt Clough, Chicago, Ill.; Mr. Emerson Foote, New York, N. Y.; and Mr. Samuel Harrell, Indianapolis, Ind., Treasurer, has been approved by the Board of Directors. Mr. Howell will serve as Chairman of the Committee.

CONGRESSIONAL HEARINGS ON HEART DISEASE LEGISLATION

Representatives of the American Heart Association, including Arlie R. Barnes, M.D., President; Charles A. R. Connor, M.D., Medical Director; David D. Rutstein, M.D.; and T. Duckett Jones, M.D., presented statements at the hearings on Bill S-2215, a bill to provide for research and control relating to diseases of the heart and circulation, before the Sub-Committee on Health of the Committee on Labor and Public Welfare of the United States Senate, on April 8th.

The Bill, which provides for the formation of a National Heart Institute in the National Institute of Health within the United States Public Health Service, received the endorsement

of the Association's representatives with several modifications. These mainly concerned the functions of the National Heart Council, which would be specifically empowered to provide the necessary guidance to the Surgeon General of the United States Public Health Service in carrying out the provisions of the Bill.

It was recommended that the powers of the National Heart Council be made similar to those of the National Advisory Cancer Committee, and that it be authorized to (1) review research projects or programs and recommend to the Surgeon General such projects it believed to show promise of making valuable contributions to human knowledge; (2) review applications for grants-in-aid of research and demonstration projects and certify to the Surgeon General its approval of such projects; (3) review applications for grants-in-aid for training and instruction and certify to the Surgeon General its approval of such applications; and (4) advise, consult with, and make recommendations to the Surgeon General with respect to carrying out the provisions of this Act.

It was also recommended that six of the twelve Council Members be selected from leading medical or scientific authorities who are outstanding in the study, diagnosis, and treatment of cardiovascular diseases.

The testimony presented by Doctors Barnes, Connor, Rutstein, and Jones was in accord with the action taken by the Executive Committee of the Association on May 5, 1947, in approving many of the provisions of the Bill (HR 3762) presented by Representative K. Javits of New York.

The Javits Bill, as well as other suggested legislation relating to research in diseases of the heart and blood vessels, received public hearings before the Committee of Interstate and Foreign Commerce of the House of Representatives on May 5 and 6, 1948. Action taken on Senate and House bills will be reported in future issues of the JOURNAL.

PAUL WHITEMAN CONTEST

Public contributions made to the American Heart Association through the American Council on Rheumatic Fever in the Paul Whiteman "Memory Tune Contest" have amounted to approximately $25,250. The contest, which was broadcast over the American Broadcasting Company network, ran for four weeks beginning March 1. More than 119,000 letters were entered in the contest.

RESEARCH GRANTS

The Life Insurance Medical Research Fund has announced the award of forty-three grants-in-aid of research in the field of cardiovascular disease and fourteen postgraduate fellowships for research. The total sum granted for research programs is $484,790. The amount awarded with fellowships is $52,600. Postgraduate fellowship stipends vary from $2,500 to $4,000.

These awards bring the total sum made available for aid to medical research by the Life Insurance Medical Research Fund since its organization in December, 1945, to approximately $1,800,000.

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